EXHIBIT A

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(57) **Abstract** (Modified)
Elements of the Invention The condensation diazepine derivative shown by the formula (I), or its salt.

(However, the notation in a formula shows following semantics.) A ring : The benzene ring or a thiophene ring, an R1:hydrogen atom, a low-grade alkyl group, or an aralkyl radical, R2: A low-grade alkyl group, an aralkyl radical or a phenyl group, L1 : Association or an alkylene group, X : Association, -CO- or -NHCO-, R3, an R5:aralkyl radical, or a low-grade alkyl group, L2: -- the heterocycle of 3 containing formula-(CHOH) n- or formula-CONHCHR5-, n:1 or 2, Y:-Het, -CH2-Het, -CH2-S-Het or -CO2-R4, Het:1, or four nitrogen atoms thru/or 6 members, an R4:hydrogen atom, or low-grade alkyl group.
Effect It has specific and powerful inhibition activity to Homo sapiens renin, and is useful as a prevention / therapy agent to hypertension, especially renin-angiotensin dependency hypertension.

Claim(s)
Claim 1 The condensation diazepine derivative shown by the following general formula (I), or its salt.
Formula 1

(However, the notation in a formula shows following semantics.)
A ring : The benzene ring or the thiophene ring which may be permuted, an R1:hydrogen atom, A low-grade alkyl group or an aralkyl radical, R2 : A low-grade alkyl group, an aralkyl radical, or the phenyl group that may be permuted, L1 : The alkylene group which may be permuted by association, the low-grade alkyl group, or the aralkyl radical, X : The radical shown by the radical shown by association and formula-CO-, or formula-NHCO-, R3 : The low-grade alkyl group which may be permuted by the aralkyl radical or the cycloalkyl radical, L2 : The radical shown by the radical shown by formula-(CHOH) n-, or formula-CONHCHR5-, n:1 or 2, R5 : The low-grade alkyl group which may be permuted by the aralkyl radical or the cycloalkyl radical, Y:-Het, -CH2-Het, -CH2-S-Het, or -CO2- the heterocycle of R4, 3 which the Het:permutation of may be done and contains 1 thru/or four nitrogen atoms, or 6 members, an R4:hydrogen atom, or low-grade alkyl group.
Claim 2 The condensation diazepine derivative according to claim 1 which L2 is the radical shown by formula-(CHOH) n-, and is the tetrazolyl group or 2-oxo--oxazolidinyl radical by which Het may be permuted, or its salt.

Detailed Description of the Invention
0001
Industrial Application This invention relates to physic, a condensation diazepine derivative especially useful as a hypertension prevention therapy agent, or its salt.
0002
Description of the Prior Art A renin inhibitor tends to control generation of angiotensin II which works powerfully to pressure ups, such as a vasoconstrictor action and aldosterone secretion, by checking the reaction of the renin and the renin substrate (angiotensinogen) which are called rate-determining step of the renin-angiotensin series which is a pressure-up system in the living body, and reducing generation of angiotensin I.

0003 In research of the latest renin inhibitor, SUTACHIN of the specific amino acid contained in the pepstatin of a natural renin inhibitor thinks that they are Leu-Val of a renin substrate analog, and the transition state of a Leu-Leu part (hydrolysis part by renin), and the transition state analog (Transition-state analogs) which introduced SUTACHIN into the synthetic renin substrate analog attracts attention. It is contained under the category of this transition state analog, and the peptides indicated by JP,64-19071,A, JP,4-279572,A, J.Med.Chem., 35, 1735-1746 (1992), etc. are mentioned as the newest renin inhibitor which should be observed.

0004

Problem(s) to be Solved by the Invention In order to be able to use a renin inhibitor on clinical (1) It has powerful inhibition activity to Homo sapiens renin (2) There is durability of reaction time suitable for clinical (3) It excels in absorptivity from an intestinal tract (4) To be the renin inhibitor equipped with the singularity of the inhibition activity over Homo sapiens renin being high is demanded.

0005 making the problem of enhancement of inhibition activity into the transition state analog which introduced SUTACHIN -- moreover, by introducing a protective group into the amino terminal and/or C terminal of a peptide about the problem of duration-of-action-izing, further, by optimizing each side chain about the problem of singularity enhancement, the good result is produced and it can say **that the temporary solution direction has been given and** .

0006 However, about an intestinal tract absorptivity improvement, it is still unsolved. That is, for an intestinal tract absorptivity improvement, depolymerize is just going to be taken into consideration more, and it is changing to more low-molecular tripeptide and a more low-molecular dipeptide also in the development research of a transition state analog. Although the peptides of said publication are these typical compounds, this application compound is the nonpeptidic renin inhibitor found out for the purpose of the further depolymerize. Moreover, although a compound given in JP,2-204491,A, JP,4-230380,A, and JP,5-239059,A is also nonpeptidic, it differs in this application compound and the chemical structure.

0007

Means for Solving the Problem Under such a technical level, as a result of inquiring wholeheartedly for the purpose of offer of the renin inhibitor which can respond to the request of aforementioned (1) - (4), by introducing a condensation diazepine ring as a transition state analog, this invention persons discovered that the above-mentioned purpose achievement was aimed at also unexpectedly, and completed this invention. That is, this invention relates to the condensation diazepine derivative shown by the following general formula (I), or its salt.

0008

Formula 2

0009 (However, the notation in a formula shows following semantics.)
A ring : The benzene ring or the thiophene ring which may be permuted, an R1:hydrogen atom, A low-grade alkyl group or an aralkyl radical, R2 : A low-grade alkyl group, an aralkyl radical, or the phenyl group that may be permuted, L1 : The alkylene group which may be permuted by association, the low-grade alkyl group, or the aralkyl radical, X : The radical shown by the radical shown by association and formula-CO-, or formula-NHCO-, R3 : The

low-grade alkyl group which may be permuted by the aralkyl radical or the cycloalkyl radical, L2 : The radical shown by the radical shown by formula-(CHOH) n-, or formula-CONHCHR5-, n:1 or 2, R5 : The low-grade alkyl group which may be permuted by the aralkyl radical or the cycloalkyl radical, Y:-Het, -CH2-Het, -CH2-S-Het, or -CO2- the heterocycle of R4, 3 which the Het:permutation of may be done and contains 1 thru/or four nitrogen atoms, or 6 members, an R4:hydrogen atom, or low-grade alkyl group. Moreover, in this invention, it is desirable that L2 is the radical shown by formula-(CHOH) n-, and it is the tetrazolyl group or 2-oxo--oxazolidinyl radical by which Het may be permuted.
0010 Hereafter, it explains in full detail about this invention compound (I). When X is the radical shown by formula-CO-, this invention compound is an amide derivative (IIa). Moreover, when X is the radical shown by formula-NHCO-, this invention compound is an urea derivative (IIb). Furthermore, when X is association, this invention compound is secondary amine (IIc).
0011
Formula 3

0012 (A ring, and R1, R2, R3, L1, L2 and Y have above semantics among a formula.) Unless it refuses especially in the definition of the general formula of this specification, the vocabulary "low-grade" Becoming means the chain of the shape of the shape of a straight chain of 1-6 carbon numbers, and branching. As a "low-grade alkyl group", specifically Therefore, for example, a methyl group, An ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, sec-butyl, tert-butyl, a pentyl radical, an isopentyl radical, A neopentyl radical, a tert-pentyl radical, 1-methylbutyl radical, 2-methylbutyl radical, 1, 2-dimethyl propyl group, a hexyl group, an iso hexyl group, 1-methyl pentyl radical, 2-methyl pentyl radical, 3-methyl pentyl radical, 1, and 1-dimethyl butyl, 1, 2-dimethyl butyl, 2, and 2-dimethyl butyl, 1, 3-dimethyl butyl, 2, 3-dimethyl butyl, 3, and 3-dimethyl butyl, 1-ethyl butyl, 2-ethyl butyl, 1 and 1, a 2-trimethyl propyl group, 1 and 2, a 2-trimethyl propyl

group, a 1-ethyl-1-methylpropyl radical, a 1-ethyl-2-methylpropyl radical, etc. are mentioned. The alkyl group of 1-4 has desirable carbon numbers, such as a methyl group, an ethyl group, a propyl group, an isopropyl group, and butyl, among these radicals, a methyl group and an ethyl group are more desirable, and a methyl group is still more desirable.

0013 As a "low-grade alkylene group", the alkylene group whose carbon numbers are 1 thru/or six pieces is mentioned, and, specifically, a methylene group, ethylene, a methyl methylene group, a trimethylene radical, a dimethyl methylene group, a tetramethylen radical, a methyl trimethylene radical, ethyl ethylene, dimethyl ethylene, an ethyl methyl methylene group, a pentamethylene radical, a methyl tetramethylen radical, a dimethyl trimethylene radical, a trimethylethylene radical, a diethyl methylene group, a hexamethylene radical, a methyl pentamethylene radical, a dimethyl tetramethylen radical, etc. are mentioned. The alkylene group of 1 thru/or 3 has the desirable carbon number of a methylene group, ethylene, a methyl methylene group, a trimethylene radical, and a dimethyl methylene group among these radicals, a methylene group and ethylene are more desirable, and a methylene group is still more desirable.

0014 An "aralkyl radical" means the radical by which the hydrogen of the arbitration of the above "a low-grade alkyl group" was permuted by the aryl group. Although an "aryl group" means an aromatic hydrocarbon radical, a carbon number 6 thru/or its 14 aryl groups are desirable. It is a phenyl group, a tolyl group, a xylyl group, a biphenyl radical, a naphthyl group, an indenyl group, an anthryl radical, and a phenan tolyl group, and, specifically, they are a phenyl group or a naphthyl group still more preferably. A "cycloalkyl radical" means the annular alkyl group whose carbon numbers are 3 thru/or seven pieces, and a cyclo propyl group, cyclo butyl, a cyclopentylic group, a cyclohexyl radical, a cycloheptyl radical, etc. are mentioned as an example.

0015 "Heterocycle of 3 containing 1 thru/or four nitrogen atoms thru/or 6 members" may contain the oxygen atom or the nitrogen atom further. Specifically, you may be a pyrrolyl radical, a pyrrolidinyl radical, a pyridyl radical, an imidazolyl radical, a piperazinyl radical, a pyrazolyl radical, a pyrazinyl radical, a pyrimidinyl group, a pilus DAJINIRU radical, a pyrrolidinyl radical, a piperidinyl radical, a piperazinyl radical, an imidazolidinyl radical, a gay piperazinyl radical, a PIRAZORIJINIRU radical, a thoriadinyl group, a tetrazolyl group, etc. Moreover, it considers as the heterocycle also containing an oxygen atom, and an oxazolyl radical, an oxazolidinyl radical, an iso oxazolyl radical, etc. are mentioned. Furthermore, it considers as the heterocycle also containing a sulfur atom, and a thiazolyl radical, a thia ZORINIRU radical, an iso thia ZORINIRU radical, 1 and 3, 4-thiadiazolyl radical, 1 and 2, 5-thiadiazolyl radical, etc. are mentioned. As for this heterocycle, it is desirable that they are 5 thru/or 6 membered-rings. Furthermore, this invention compound may form a salt easily with an inorganic acid or an organic acid. As a salt, organic-acid salts, such as inorganic-acid salts, such as a hydrochloric acid, a hydrobromic acid, a hydroiodic acid, a sulfuric acid, a nitric acid, and a phosphoric acid, a formic acid, an acetic acid, a propionic acid, oxalic acid, a malonic acid, a succinic acid, a fumaric acid, a maleic acid, a lactic acid, a malic acid, a tartaric acid, a citric acid, methansulfonic acid, ethane sulfonic acid, an aspartic acid, and glutamic acid, can be mentioned, for example.

0016 Since this invention compound (I) has two or more asymmetric carbon atoms, the optical isomer and diastereoisomer based on an asymmetric carbon atom exist. The mixture of the thing from which these various isomers were isolated, and these isomers is contained in this invention. Moreover, although various kinds of hydrates, various solvates, a compatible isomer, a crystal polymorphism, etc. exist by the case, the compound of the thing from which these compounds were isolated, and all its mixture is contained in this invention compound.

0017 The first process of a manufacturing method **0018**

Formula 4

0019 (V and W mean leaving groups, such as a halogen atom and an imidazolyl radical, among a formula.) A ring, and R1, R2, R3, L1, L2 and Y have above semantics.
this invention compound (IIb) can be obtained by carrying out coupling of a primary amine compound (IV) and the primary amine compound (V) under existence of compounds (VI), such as a phosgene equivalence object. A phosgene, TORIHOSUGEN, carbonyldiimidazole, etc. are mentioned as a compound (VI). For example, the first process is applied in an example 1 thru/or 9 and 11 and 12 and 20 thru/or 26. Moreover, in order to promote a reaction, it may be desirable to make it react to the bottom of existence of organic bases, such as inorganic bases, such as a sodium carbonate, a sodium hydroxide, and a potassium hydroxide, triethylamine, and N.N-dimethylaniline.
0020 As for a reaction solvent, solvents usually used, such as inert solvents, such as N.N-dimethylformamide, chloroform, benzene, toluene, a xylene, dioxane, the ether, a tetrahydrofuran, dichloromethane, and a dichloroethane, or a mixed solvent of such arbitration, are used. This reaction is usually performed under a room temperature thru/or heating, stirring.
The second process **0021**
Formula 5

0022 (Pc means the protective group of a carboxyl group among a formula.) A ring, and R1, R2, R3, L1, L2 and Y have above semantics.
Condensation of a carboxylic-acid derivative (VII) and the amine derivative (VIII) is carried out, and this invention compound (IIa) is obtained. For example, the second process is applied in examples 13 and 14, an example 17 or 19, 27, or 29. The amino terminus of an amine derivative (VIII) may be protected by the protective group (Pa). Before this protective group (Pa) carries out a condensation reaction, deprotection of it is carried out by the contact hydrogenation reaction etc.
0023 Activity ester may be used and condensed instead of a carboxylic-acid derivative. Phenol systems, such as p-nitrophenol, N-hydroxysuccinimide, Activity ester which is made to react with the compound of N-hydroxylamine systems, such as 1-hydroxy benzotriazol, and is obtained; Carbonic acid monoalkyl ester, Or the mixed acid anhydride and chlorination diphenyl phosphoryl which are made to react with an organic acid and are obtained, Ester The phosphoric-acid system mixed acid anhydride which N-methyl morpholine is made to react and is obtained; A hydrazine, Acid halide which is made to react with nitrous-acid alkyl and is obtained, such as acid azide; acid chloride and an acid star's picture; it can manufacture with the application of the C edge activating method using C edge activators, such as a symmetry mold acid anhydride.
0024 In a condensation reaction, it is desirable to use a condensing agent and it can use suitably a 1-ethyl-3-(3-(N and N-dimethylamino) propyl) carbodiimide (WSCD) as a condensing agent. In addition, the condensing agent generally used for peptide linkage formation of N and N-dicyclohexylcarbodiimide (DCC), diphenyl phosphoryl azide (DPPA), isobutyl chloro formate, carbonyldiimidazole, a benzotriazoryl-N-hydroxy tris dimethylamino HOSUHONIUMUHEKISAFURUORORIN ghost salt (Bop reagent), etc. can be used.
0025 As an additive which may be used with condensing agents, such as WSCD and DCC, there is HOBT, in addition it is N-hydroxysuccinimide (HONSu) and 3-hydroxy-4-oxo-. - It is 3 and 4-dihydro. - 1, 2, and 3-benzotriazine (HOOBt) etc. is mentioned.
0026 Moreover, it may be desirable when making it react to the bottom of existence of bases, such as triethylamine, a pyridine, and N-methyl morpholine, depending on the

approach applied advances a reaction smoothly. A reaction is usually performed to the bottom of cooling among a solvent thru/or a room temperature. As for the solvent used, solvents usually used, such as chloroform, a carbon tetrachloride, cyclo ROETAN, a tetrahydrofuran, dioxane, dimethoxymethane, dimethoxyethane, ethyl acetate, benzene, dimethylformamide, dimethyl sulfoxide, or a mixed solvent of such arbitration, are used.
0027 Pa and Pc have the good protective group usually used in the peptide field. Specifically as a protective group (Pa) of the amino group, it is benzyloxycarbonyl radical, p-nitrobenzyl oxycarbonyl radical, p-methoxybenzyl oxycarbonyl radical, p-chloro benzyloxycarbonyl radical, 1, and 1-dimethylethoxy carbonyl group, isobornyl oxycarbonyl radical, p-biphenyl isopropyloxy carbonyl group, 3, and 5-dimethoxy, for example. - alpha and alpha-dimethylbenzyl oxycarbonyl radical, 9-fluorenyl methyloxy carbonyl group, a methylsulfonyl ethoxycarbonyl radical, etc. are mentioned.
0028 Moreover, as a protective group (Pc) of a carboxyl group, permutation benzyls, such as benzyl, p-nitrobenzyl radical, p-methoxybenzyl radical, a diphenyl methyl group, and a benzhydryl group, tert-butyl, a methyl group, an ethyl group, a phenacyl radical, a trichloroethyl radical, etc. are specifically mentioned, for example.
The third process **0029**
Formula 6

0030 (A ring, and R1, R2, R3, L1, L2, R5, Y and Pc have above semantics among a formula.)
A condensation diazepine derivative (IX) is used as a start raw material, condensation is carried out to an amine derivative (X), and this invention compound (III) is obtained. The reaction condition is the same as that of the second process. As other processes, this invention compound which the low-grade alkyl group permuted by the nitrogen atom of a heterocycle radical can be obtained by applying N-alkylation reaction of a conventional method from this invention compound which the hydrogen atom has combined with the nitrogen atom.
0031 Manufacturing-technology top effectiveness-like **a suitable protective group / the carbonyl group of an intermediate-product compound or this invention compound**

/, i.e., transpose to a functional group convertible into a carbonyl group easily, in the above-mentioned manufacture approach As such a protective group, the protective group of Green (Greene) and the Wuts (Wuts) work, "Protective Groups in Organic Synthesis", and the 2nd-edition publication can be mentioned, for example, and these can be suitably used according to a reaction condition. In addition, as a functional group convertible into a carbonyl group, a hydroxy methylene group (-CH(OH)-) can be mentioned, for example, and such a functional group can also be easily used as an equivalence object of a carbonyl group.

0032 Thus, the compound according to manufactured this invention is isolated as its salt with isolation, and is refined. Isolation and purification are performed suitably with the application of the usual chemistry actuation of an extract, crystallization, recrystallization, various chromatographies, etc. moreover, the thing for which a racemic compound uses a suitable raw material compound -- or it can lead to an isomer pure in stereochemistry by general optical resolution methods (for example, the approach of leading to diastereomeric salt with common optical-activity acids (tartaric acid etc.), and carrying out optical resolution etc.). Moreover, diastereomer mixture is separable with a conventional method, for example, fractional-crystallization-izing, or a chromatography.

0033

Effect of the Invention The condensation diazepine compound of this invention or its salt has specific and powerful inhibition activity to Homo sapiens renin, and has the durability of reaction time suitable for clinical administration, and is excellent in absorptivity from the intestinal tract. Therefore, this invention compound is useful as a prevention / therapy agent to hypertension, especially renin-angiotensin dependency hypertension.

0034 The specific and powerful inhibition activity over the Homo sapiens renin of this invention compound is checked by the test method shown below.

To 250micro **of human plasma** l which has the angiotensin 1 generation activity of inhibition activity 0.5/ng/ml/hr (37 degrees C) to human plasma renin 25micro of dimethyl sulfoxide solutions l of enzyme inhibitor (BAL, 8-hydroxy sulfate, pH4.6) solution (at time **Business** 10ml adding distilled water preparation) 225microl in a commercial measurement-of-renin-activity kit (dextran charcoal method) (Green Cross Corp. make) and a sample compound is added and agitated. Carry out incubation of the part at 37 degrees C for 2 hours, and the remainder is left at 4 degrees C. It asked for the inhibition concentration IC 50 (M) 50% by sampling every **100micro / l** from each, applying to radioimmunoassay using a commercial measurement-of-renin-activity kit (dextran charcoal method), and measuring the difference of the amount of angiotensin 1 generation in 37 degrees C and 4 degrees C.

0035 Although pharmaceutical preparation which contains the condensation diazepine compound of this invention or its salt as an active principle is usually made into internal use agents, such as a tablet, a pill, and a capsule, using the support for internal use, and the additive of an excipient and others, it can also be considered as parenteral administration pharmaceutical preparation, such as injections. The clinical dose of this invention compound is suitably determined in consideration of a patient's symptom to apply, age, sex, etc., and is prescribed for the patient in 2 - 4 steps.

0036

Example In the above, although this invention compound and its manufacturing method were explained, an example explains to a detail further below. In addition, the proton nuclear-magnetic-resonance spectrum with which 1 H-NMR in an example used the tetramethylsilane for the internal standard, and MS mean a mass spectrum, and IR means an infrared absorption spectrum.

0037 example 1 (3R)-3-**3- (1S)-1-cyclohexyl methyl-2-hydroxy-3- (1-methyl-5-tetra-ZORIRU) Thio Propyl ureido**-1-methyl-5-phenyl -2, 3-dihydro-1H-1, 4-benzodiazepine-2-ON (3R)-3-amino-1-methyl-5-phenyl - 2 Three - Dihydro-1H-benzodiazepine-2-ON 133mg is dissolved in 2ml of methylene chlorides. Triethylamine

0.15ml and carbonyldiimidazole 122mg were added to this, and it stirred at the room temperature for 1 hour. (1S) -1 - What dissolved 322mg **of cyclohexyl methyl-2-hydroxy-3-(1-methyl-5-tetra-ZORIRU) thio propylamine hydrochlorides** and triethylamine 0.31ml in 4ml of methylene chlorides was added, and it stirred at the room temperature further for 2 hours. 20ml of water was added to the reaction solution, and 20ml of methylene chlorides extracted twice. The solvent was distilled off after drying an organic layer with anhydrous sodium sulfate. The silica gel column chromatography (eluate; ethyl acetate / n-hexane =3/1) refined the obtained residue, and 152mg of specified substance was obtained.

0038 1 H-NMR (CDCl3) : 0.81-1.80 (15 H;m), 3.41-3.44 (1 H;m), 3.48 (3 H;s), 3.90 (3 H;s), 4.01 (1 H;br), 4.35 (1 H;br), 5.40 (1 H;d, J= 8.8Hz), 5.44 (1 H;d, J= 8.4Hz) 6.65 (1 H;d, J= 8.4Hz), 7.21-7.63(9 H;m) MS(FAB, Pos.): 577 (M+1) examples 2 (3S)-3-**3- (-- one -- S --) - one - cyclohexyl -- methyl - two - hydroxy one - three - (1-methyl-5-tetra-ZORIRU) -- thio -- -- propyl -- -- ureido --** - one - methyl - five - phenyl - two -- three - dihydro one - one -- H - one -- four - the benzodiazepine - two - ON -- an example -- one -- being the same -- actuation -- (3R) It is (3S)-3-amino-1-methyl-5-phenyl instead of the -3-amino-1-methyl-5-phenyl -2 and 3-dihydro-1H-benzodiazepine-2-ON. - 2 Three - Dihydro-1H-benzodiazepine-2-ON 133mg is used. 150mg of specified substance was obtained.

0039 1 H-NMR (CDCl3) : 0.79-1.83 (15 H;m), 3.42-3.53 (1 H;m), 3.48 (3 H;s), 3.91 (3 H;s), 3.91-3.95 (1 H;m), 4.41 (1 H;br), 5.47 (2 H;d, J= 8.4Hz), 6.70 (1 H;d, J= 8.4Hz), 7.20-7.60(9 H;m) MS(FAB, Pos.): 577 (M+1) examples 3 (3R)-3-**3- 1S and (R 2)-1-cyclohexyl methyl-2- ((5S)-3-ethyl-2-oxo--5-oxazolidinyl)-2-hydroxyethyl ureido** by the same actuation as the -2, 3-dihydro-1-methyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 1 (1S)-1-cyclohexyl methyl-2-hydroxy-3- **Instead of a thio** propylamine hydrochloride, (1-methyl-5-tetra-ZORIRU) A 1S and (R **2**)-1-cyclohexyl methyl-2-(5S) (-3-ethyl-2-oxo--5-oxazolidinyl)-2-hydroxy ethylamine hydrochloride It used and the specified substance was obtained with 62% of yield.

0040 1 H-NMR (CDCl3) : 0.76-1.82 (13 H;m), 1.14 (3 H;t, J= 8.8Hz) 3.26-3.31 (2 H;m), 3.49 (3 H;s), 3.48-3.56 (1 H;m), 3.62-3.66 (2 H;m), 4.44-4.48 (2 H;m), 5.31-5.48 (1 H;m), 5.42 (1 H;d, J= 8.4Hz) 5.88 (1 H;d, J= 7.6Hz), 6.82 (1 H;d, J= 8.4Hz), 7.22-7.69(9H, m) MS(FAB, Pos.): 562 (M+1) examples 4 (3R)-3-**3- 1S and (R 2)-1-cyclohexyl methyl-2- ((5R)-3-ethyl-2-oxo--5-oxazolidinyl)-2-hydroxyethyl ureido** by the same actuation as the -2, 3-dihydro-1-methyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 1 (1S)-1-cyclohexyl methyl-2-hydroxy-3- **Instead of a thio** propylamine hydrochloride, (1-methyl-5-tetra-ZORIRU) A 1S and (R **2**)-1-cyclohexyl methyl-2-(5R) (-3-ethyl-2-oxo--5-oxazolidinyl)-2-hydroxy ethylamine hydrochloride It used and the specified substance was obtained with 47% of yield.

0041 1H-NMR(CDCl3): 0.81-1.81(13H;m), 1.09(3H;t,J=6.8Hz), 3.21-3.32(2H;m), 3.48(3H;s), 3.52-3.57(1H;m), 3.65-3.69(1H;m), 3.93-3.99(1H;m), 4.46(2H;q,J=7.2Hz), 5.32(1H;d,J=10.0Hz), 3.39(1H;d,J=10.0Hz), 6.59(1H;d,J=8.4Hz), 7.21-7.67(9H,m)MS(FAB,Pos.): 562(M+1 example By the same actuation as the 5(3R)-3-**3-(1S) -1-cyclohexyl methyl-2-hydroxy-2-isopropyl oxycarbonyl ethyl ureido**-2, 3-dihydro-1-methyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 1 (1S) -1 - Instead of a cyclohexyl methyl-2-hydroxy-3-**(1-methyl-5-tetra-ZORIRU) thio** propylamine hydrochloride, a 3-amino-(3S)-3-cyclohexyl methyl-2-hydroxy propionic-acid isopropyl ester hydrochloride It used and the specified substance was obtained with 71% of yield.

0042 1 H-NMR (CDCl3) : 0.78-1.84 (17 H;m), 3.16 (2 H;br), 3.46 (3 H;s), 3.98 (1 H;br), 4.11 (1 H;br) 5.02-5.24 (3 H;m), 5.42 (1 H;d, J= 8.1Hz), 6.43 (1 H;d, J= 8.1Hz), 7.18-7.68(9 H;m) MS(FAB, Pos.): 535(M++1) IR numax(KBr) cm-1 : 3398, 2992, 1740, and 1680 examples 6(3R)-3-**3-(by the same actuation as the 1S, 2R-1-cyclohexyl methyl -2, 3-dihydroxy-4-(morpholino) butyl ureido**-2, 3-dihydro-1-methyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 1) Triethylamine And (1S) -1 - Instead of a cyclohexyl

methyl-2-hydroxy-3-**(1-methyl-5-tetra-ZORIRU) thio** propylamine hydrochloride, diisopropyl ethylamine and (1S) -1-cyclohexyl methyl -2, 3-dihydroxy-4- (4-morpholino) The specified substance was obtained with 59% of yield using the butylamine hydrochloride.
0043 1H-NMR(CDCl3): delta: 0.89-1.70 (14 H;m), 2.56-2.86 (8 H;m), 3.43-3.56 (2 H;m), 3.52 (3 H;s) 3.70-3.72 (2 H;m) 4.17-4.22 (1 H;m), 5.13 (1 H;br) 5.40 (1 H;d, J= 8.8Hz), 5.68 (1 H;d, J= 9.2Hz) 6.90 (1 H;d, J= 8.8Hz), 7.24-7.63(9 H;m) MS(FAB): 578 (M++1) examples 7(3R)-N-(2, 3-dihydro-1-methyl-5-phenyl-1H-1, 4-benzodiazepine-2-ON-3-IRU) aminocarbonyl-L-leucyl-L-leucine By the same actuation as the methyl ester example 1 (1S) -1 - It is L-leucyl-L-leucine instead of a cyclohexyl methyl-2-hydroxy-3-**(1-methyl-5-tetra-ZORIRU) thio** propylamine hydrochloride. The specified substance was obtained with 44% of yield using the methyl ester hydrochloride.
0044 1 H-NMR (CDCl3) : 0.84-0.97 (12 H;m), 1.48-1.82 (6 H;m), 3.46 (3 H;s), 3.69 (3 H;s), 4.27-4.37 (1 H;m), 4.53-4.57 (1 H;m), 5.41 (1 H;d, J= 8.0Hz) 5.72 (1 H;d, J= 8.0Hz), 6.71 (2 H;br), 7.20-7.61(9 H;m) MS(FAB, Pos.): 550(M++1) IR numax(KBr) cm-1 : 3364, 2968, 1750, and 1648 examples 8(3R)-N-(2, 3-dihydro-1-methyl-5-phenyl-1H-1, 4-benzodiazepine-2-ON-3-IRU) aminocarbonyl-L-phenyl alanyl-L-phenylalanine By the same actuation as the methyl ester example 1 (1S) -1 - It is L-phenyl alanyl-L-phenylalanine instead of a cyclohexyl methyl-2-hydroxy-3-**(1-methyl-5-tetra-ZORIRU) thio** propylamine hydrochloride. The specified substance was obtained with 68% of yield using the methyl ester hydrochloride.
0045 1 H-NMR (CDCl3) : 2.92-3.16 (4 H;m), 3.58 (3 H;s), 3.70 (3 H;s), 4.11 (1 H;q, J= 7.2Hz), 4.59 (1 H;q, J= 7.2Hz) 4.89 (1 H;dd, J= 6.8Hz), 5.40 (1 H;d, J= 8Hz) 6.15 (1 H;d, J= 8Hz), 6.75 (1 H;d, 8Hz) 6.96-7.45 (16 H;m), 7.54-7.62 (2 H;m), 7.75(1 H;d, J= 8Hz) MS(FAB): 618 (M++1) examples 9(3R)-N-(2, 3-dihydro-1-methyl-5-phenyl-1H-1, 4-benzodiazepine-2-ON-3-IRU) aminocarbonyl-L-leucyl-L-valine By the same actuation as the methyl ester example 1 (1S) -1 - It is L-leucyl-L-valine instead of a cyclohexyl methyl-2-hydroxy-3-**(1-methyl-5-tetra-ZORIRU) thio** propylamine hydrochloride. The specified substance was obtained with 82% of yield using the methyl ester hydrochloride.
0046 MS(FAB): 536(M++1)
IR numax KBrcm-1 : 3340, 2972, 1748, and 1648 examples 103- **(1S)-1-cyclohexyl methyl-2-hydroxy-3- (1-methyl-5-tetra-ZORIRU) Thio propyl amino** -2, 3-dihydro-5-phenyl-1H-1, 4-benzodiazepine-2-ON 2, 3-dihydro-3-hydroxy-5-phenyl-1H-1, and 4-benzodiazepine-2-ON 1.00g It dissolved in 10ml of thionyl chlorides, and heating reflux was carried out for 40 minutes. Residue is dissolved in 1,4-dioxane 10ml after distilling off a solvent, and it is (1S)-1 to this. - What dissolved 2.20g **of cyclohexyl methyl-2-hydroxy-3-(1-methyl-5-tetra-ZORIRU) thio propylamine hydrochlorides** and triethylamine 3.31ml in 1,4-dioxane 30ml was added, and it stirred at the room temperature overnight. The reaction solution was opened in 200ml of water, and 200ml of ethyl acetate extracted twice. After 200ml of saturation sodium-hydrogencarbonate water, 200ml of water, and 200ml of saturation brine washed the organic layer, it dried with anhydrous sodium sulfate and the solvent was distilled off. The silica gel column chromatography (eluate; ethyl acetate / n-hexane =1/1) refined the obtained residue, and 1.53g of specified substance was obtained.
0047 1 H-NMR (CDCl3) : 0.75-1.76 (12 H;m), 1.90 (1 H;d, J= 8.2Hz) 2.88-2.92 (1 H;m), 3.19-3.78 (4 H;m), 3.89 (1.3 H;s), 3.93 (1.7 H;s), 4.38 (0.4 H;s), 4.44 (0.6 H;s), 4.68 (0.4 H;br), 5.27 (0.6 H;br), 7.19-7.58 (9 H;m), 9.20(1 H;s) MS(FAB, Pos.): 520 (M+1) examples 113-**3- (1S)-1-cyclohexyl methyl-2-hydroxy-3-(1-methyl-5-tetra-ZORIRU) thio propyl ureido** methyl-2, 3-dihydro-5-phenyl-1H-1, and 4-benzodiazepine-2-on-carbonyldiimidazole 122mg -- And after dissolving triethylamine 0.15ml in 2ml of methylene chlorides and dropping 3-aminomethyl -2 and 2ml solution of 3-dihydro-5-phenyl-1 H-1 and 4-benzodiazepine-2-ON 133mg methylene chlorides, it stirred at the room temperature for 1 hour. (1S) -1 - What dissolved 322mg **of cyclohexyl methyl-2-hydroxy-3-(1-methyl-5-tetra-ZORIRU) thio propylamine hydrochlorides** and triethylamine 0.31ml in 4ml of

methylene chlorides was added, and it stirred at the room temperature further overnight. 50ml of water was added to the reaction solution, and 50ml of ethyl acetate extracted twice. After 200ml of saturation sodium-hydrogencarbonate water, 200ml of water, and 200ml of saturation brine washed the organic layer, it dried with anhydrous sodium sulfate and the solvent was distilled off. The silica gel column chromatography (eluate; ethyl acetate / n-hexane =5/1 - ethyl acetate) refined the obtained residue, and 130mg of specified substance was obtained.

0048 1 H-NMR (CDCl3) : 0.76-1.78 (13 H;m), 3.36-3.51 (2 H;m) and 3. -- 82 and 3.90 (3 H;s) -- 3.75-4.12 (5 H;m), 4.23 (1 H;br), and 5. -- 05 and 5.77 (1 H;d, J= 5.4Hz) -- 5.97-6.01 (1 H;m), 7.13-7.56 (9 H;m), 9.16(1 H;s) MS(FAB, Pos.): 577 (M+1) examples 123-**3-(-- one -- S --) - one - cyclohexyl -- methyl - two - hydroxy one - three - (1-methyl-5-tetra-ZORIRU) -- thio -- -- propyl -- -- ureido -- -- methyl --** - one - methyl - five - phenyl - two -- three - dihydro one - one -- H - one -- four - the benzodiazepine - two - ON -- an example -- 11 -- being the same -- actuation -- 3-aminomethyl -2, 3-dihydro-1-methyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON was used instead of 3-aminomethyl -2, 3-dihydro-5-phenyl-1H-1, and 4-benzodiazepine-2-ON, and the specified substance was obtained with 36% of yield.

0049 1 H-NMR (CDCl3) : 0.77-1.73 (13 H;m), 3.33-3.45 (2 H;m), 3.44 (3 H;s), 3.75 (1 H;dd, J= 6.4Hz, 14.4Hz), 3.83-3.93 (1 H;m), 3.90 (3 H;s), 3.99-4.04 (2 H;q, J= 6.4Hz), 4.13-4.23 (2 H;m), 5.31 (1 H;br), 6.85 (1 H;br), 7.08-7.69(9 H;m) MS(FAB, Pos.): 591 (M+1) examples 133- **N-(1S) -1-cyclohexyl methyl-2-hydroxy-3-(1-methyl-5-tetra-ZORIRU) thio propyl carbamoyl methyl** -2, 3-dihydro-5-phenyl-1H-1, and 4-benzodiazepine-2-ON (1 --) N-t-butyloxy carbonyl-L-asparatic acid alpha-2 - Benzophenone amide beta-benzyl ester 2-amino benzophenone 2.77g is dissolved in dimethyl formamide 130ml. 1-hydroxy benzotriazol 2.10g, N-t-butoxycarbonyl-L-asparatic acid beta-benzyl ester 5.00g and N, and N'-dicyclohexylcarbodiimide 3.26g was added, and it stirred at the room temperature overnight. The reaction solution was filtered and the solvent was distilled off. Ethyl acetate was added to the obtained residue, it filtered again, and the solvent was distilled off. After it dissolved the obtained residue in 200ml of ethyl acetate and 200ml of saturation sodium-hydrogencarbonate water, 200ml of water, and 200ml of saturation brine washed, it dried with anhydrous sodium sulfate and the solvent was distilled off. The silica gel column chromatography (eluate; ethyl acetate / n-hexane =1 / 5 - 1/3) refined the obtained residue, and 1.88g of specified substance was obtained.

0050 1H-NMR(CDCl3): 1.48(9H;s), 2.83(1H;d,J=17.2Hz), 3.28(1H;d,J=16.8Hz), 4.72(1H;br), 5.12(2H;dd,J=25.6Hz,12.8Hz), 5.79(1H;br), 7.10(1H;t,J=7.6Hz),7.32(5H;s), 7.47(2H;t,J=7.6Hz), 7.54-7.60(3H;m), 7.69(2H;d,J=6.8Hz), 8.62(1H;d,J=8.8Hz), 11.60(1H;s)(2) L-aspartic acid alpha-2-benzophenone amide beta-benzyl ester N-t-butyloxy carbonyl-L-asparatic acid alpha-2-benzophenone amide beta-benzyl ester 1.86g It dissolved in 4 convention hydrogen chloride dioxane 40ml, and stirred at the room temperature for 1 hour. It dissolved in 200ml of ethyl acetate, and 200ml of saturation sodium-hydrogencarbonate water, 200ml of water, and 200ml of saturation brine washed the residue which condensed the reaction solution and was obtained. The solvent after desiccation was distilled off for the organic layer with anhydrous sodium sulfate, and 1.43g of specified substance was obtained.

0051 1 H-NMR (CDCl3) : 2.84-3.02 (2 H;m), 3.86 (1 H;br), 5.14 (2H, s), 7.00-7.77 (8 H;m), 7.30 (5 H;s) 8.61 (1 H;d, J= 8.0Hz), 11.92(1H, s) MS (FAB, Pos.) : 403 (M+1), -- 385 (M+1-H2O) (3) Benzyl 2- () (3S) -2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU acetate L-asparatic acid alpha-2-benzophenone amide beta-benzyl ester 1.43g is dissolved in 30ml of acetic acids. 1.29g of ammonium acetate In addition, it stirred at 50 degrees C for 2 hours and 45 minutes. It dissolved in 50ml of ethyl acetate, and 50ml of saturation sodium-hydrogencarbonate water, 50ml of water, and 50ml of saturation brine washed the residue which condensed the reaction solution and was obtained. The solvent after desiccation was distilled off for the organic layer with anhydrous

sodium sulfate. The obtained residue was crystallized by ethyl acetate / n-hexane, and 0.47g of specified substance was obtained.
0052 1 H-NMR (CDCl3) : 3.38 (1 H;dd, J= 54.0, 10.8Hz), 3.42 (1 H;dd, J= 54.0, 10.8Hz) 4.22 (1 H;t, J= 5.4Hz), 5.20 (2 H;s) 7.14-7.56 (14 H;m), 8.74(1H, s) MS (EI, In Beam) : 384 (M+) (4) N-t-butyloxy carbonyl-D-aspartic acid By the same actuation as the alpha-2-benzophenone amide beta-benzyl ester example 13 (1) N-t-butoxycarbonyl-L-asparatic acid It is an N-t-butoxycarbonyl-D-aspartic acid instead of beta-benzyl ester. The specified substance was obtained with 43% of yield using beta-benzyl ester.
0053 1 H-NMR (CDCl3) : 1.48 (9 H;s) 2.83 (1 H;dd, J= 16.2Hz, 5.4Hz), 3.27 (1 H;dd, J= 16.2, 5.4Hz) 4.72-4.76 (1H, m), 5.13 (2 H;dd, J= 18.9, 13.5Hz) 5.82 (1 H;d, J= 10.8Hz), 7.11 (1 H;t, J= 8.1Hz) 7.28-7.72 (12 H;m), 8.64 (1 H;d, J= 10.8Hz), 11.60(1 H;s) MS (FAB, Pos) : 503 (M+1) (5) D-aspartic acid alpha-2-benzophenone amide By the same actuation as beta-benzyl ester example 13 (2) N-t-butyloxy carbonyl-L-asparatic acid alpha-2-benzophenone amide It is a N-t-butyloxy carbonyl-D-aspartic acid instead of beta-benzyl ester. alpha-2-benzophenone amide beta-benzyl ester It used and the specified substance was obtained with 96% of yield.
0054 1 H-NMR (CDCl3) : 2.65-3.01 (2 H;m), 3.84 (1 H;br), 5.12 (2H, s), 7.00-7.77 (8 H;m), 7.30 (5 H;s) 8.62 (1 H;d, J= 8.0Hz), 11.92(1 H;s) MS (FAB, Pos) : 403 (M+1) (6) Benzyl By the same actuation as 2-(3R) (-2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) acetate example 13 (3) L-asparatic acid alpha-2-benzophenone amide It is a D-aspartic-acid alpha-2-benzophenone amide instead of beta-benzyl ester. The specified substance was obtained with 28% of yield using beta-benzyl ester.
0055 1 H-NMR (CDCl3) : 3.39 (2 H;dd, J= 7.1, 5.2Hz), 4.12 (1 H;t, J= 7.1Hz) 5.19 (2 H;s), 7.12-7.48 (9 H;m), 7.34 (5 H;s), 9.40(1 H;s) MS () **EI, In** Beam: 384 (M+) (7) 2-(2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) benzyl acetate 2-(3S) (-2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) acetate and benzyl 0.38g of equivalent mixture of 2-(3R) (-2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) acetate is dissolved in ethanol 30ml. 10% palladium / about 30mg of carbon, and 1.5ml of formic acid were added, and it stirred at 50 degrees C for 3 hours. The reaction solution was filtered using talc and the solvent was distilled off. The obtained residue was crystallized using the ether n-hexane and 0.20g of specified substance was obtained.
0056 1 H-NMR (CDCl3-CD3OD) : 3.02 (1 H;dd, J= 18.9, 8.1Hz), 3.26 (1 H;dd, J= 21.6, 10.8Hz) 3.97 (1 H;t, J= 8.1Hz), 7.16-7.60 (9 H;m), 10.60(1 H;s) MS () **EI, In** Beam: 294 (M+) (8) 3-**N- (1S)-1-cyclohexyl methyl-2-hydroxy-3- (1-methyl-5-tetra-ZORIRU) Thio propyl carbamoyl methyl** -2, 3-dihydro-5-phenyl-1H-1, 4-benzodiazepine-2-ON (1S) - 1-cyclohexyl methyl-2-hydroxy-3- **240mg of thio** propylamine hydrochlorides is dissolved in dimethyl formamide 2ml. (1-methyl-5-tetra-ZORIRU) To this, triethylamine 0.23ml, the dimethyl formamide 2ml solution of 0.20g of 2-(2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) acetic acids, And diphenyl phosphoric-acid azide 0.18ml was added one by one, and it stirred for three days at the room temperature. The reaction solution was opened in 50ml of saturation sodium-hydrogencarbonate water solutions, and it extracted by ethyl-acetate 50mlx2. Sequential washing of the organic layer was carried out by 50ml of water, and 50ml of saturation brine, and the solvent was distilled off after drying with anhydrous sodium sulfate. The silica gel column chromatography (eluate: ethyl acetate / n-hexane =2 / 1 - 3/1) refined the obtained residue, and 0.12g of high polar compounds and 0.16g of low polar compounds were obtained.
0057 High polar compound Rf value 0.10 (ethyl acetate / n-hexane = 2/1)
1H-NMR(CDCl3): 0.79-0/96(3H;m), 1.10-1.41(5H;m), 1.54-1.61(4H;m), 1.78(1H;d,J=12.4Hz), 3.06(1H;dd,J=14.8,5.6Hz), 3.24(1H;dd,J=14.8,7.2Hz), 3.36-3.51(2H;m), 3.80-3.85(1H;m), 3.87(3H;s), 4.11-4.24(2H;m), 4.34(1H;d,J=4.4Hz), 6.96(1H;d,J=9.6Hz), 7.13-7.53 (9 H;m), 9.01(1 H;s) MS (FAB, Pos.) : 562 (M+1) low polar compound Rf value 0.16 (ethyl acetate / n-hexane = 2/1)
1 H-NMR (CDCl3) : 0.74-0.93 (3 H;m), 1.07-1.41 (5 H;m), 1.54-1.66 (4 H;m), 1.78 (1 H;d,

J= 12.4Hz) 3.14 (1 H;d, J= 6.0Hz), 3.34-3.49 (2 H;m), 3.81 (3 H;s), 3.87-3.94 (1 H;m), 4.06-4.15 (3 H;m), 4.47 (1 H;d, J= 4.4Hz), 7.15-7.54 (9 H;m), 8.65(1 H;s) MS(FAB, Pos.): 562 (M+1) examples 143- **N-(1S) -1-cyclohexyl methyl-2-hydroxy-3-(1-methyl-5-tetra-ZORIRU) thio propyl carbamoyl methyl** -2, 3-dihydro-1-methyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON (1 --) benzyl 48mg (60% content) of 2-(2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) acetate sodium hydride is suspended in dimethyl formamide 2ml. this -- benzyl 2- () (3S) -2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU acetate and benzyl The dimethyl formamide 4ml solution of 0.38g of equivalent mixture of 2-(3R) (-2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) acetate is added. It stirred at the room temperature for 30 minutes. Iodine methyl 0.09ml was added to this, and it stirred at the room temperature for 20 minutes. The reaction mixture was opened in 100ml of iced water, and it extracted in ethyl-acetate 100mlx2. Sequential washing of the organic layer was carried out by 100ml of saturation sodium-hydrogencarbonate water solutions, 100ml of water, and 100ml of saturation brine, and the solvent was distilled off after drying with anhydrous sodium sulfate. The silica gel column chromatography (eluate: ethyl acetate / benzene =1 / 20 - 1/10) refined the obtained residue, and 0.39g of specified substance was obtained.

0058 1 H-NMR (CDCl3) : 3.10-3.50 (2 H;m), 3.40 (3 H;s) 4.15 (1 H;t, J= 7.2Hz), 5.12 (2 H;s), 7.11-7.56(14 H;m) MS (EI, In Beam) : 398 (M+) (2) By the same actuation as 2-(2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) acetic-acid example 13 (7) Benzyl 2- () (3S) -2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU acetate and benzyl 2- () instead of **of the equivalent mixture of (3R)-2, 3-dihydro-2-oxo--5-phenyl-1H-1, and 4-benzodiazepine-3-IRU acetate** -- benzyl 2- (2 and 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1 --) The specified substance was obtained with 64% of yield using 4-benzodiazepine-3-IRU acetate.

0059 1 H-NMR (DMSO-d6) : 2.79-3.26 (2 H;m), 3.35 (3 H;s) 3.94 (1 H;t, J= 6.9Hz), 7.21-7.72(9 H;m) MS () **EI, In** Beam: 308 (M+) (3) 3-**N- (1S)-1-cyclohexyl methyl-2-hydroxy-3- (1-methyl-5-tetra-ZORIRU) Thio propyl carbamoyl methyl** by the same actuation as the -2, 3-dihydro-1-methyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 13 (8) Instead of 2-(2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) acetic acid, 2-(2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) acetic acid It used and the specified substance was obtained with 64% of yield (0.13g of high polar compounds, 0.14g of low polar compounds).

0060 High polar compound Rf value 0.11 (ethyl acetate / n-hexane = 2/1)
1H-NMR(CDCl3): 0.78-0.96(3H;m), 1.10-1.41(5H;m), 1.60-1.68(4H;m), 1.79(1H;d,J=12.8Hz), 3.09(1H;dd,J=21.2,14.4Hz), 3.11(1H;dd,J=21.6,14.8Hz), 3.42(3H;s), 3.38-3.50(2H;m), 3.91(3H;s), 4.09-4.16(3H;m), 6.99(1H;d,J=9.6Hz), 7.20-7.61(9H;m)MS(FAB,Pos.): 576 (M+1) low-polar compound Rf value 0.20 (ethyl acetate / n-hexane = 2/1)
1H-NMR(CDCl3): 0.79-0.93(3H;m), 1.12-1.42(5H;m), 1.62-1.65(4H;m), 1.77(1H;d,J=20.4Hz), 3.09(1H;dd,J=14.4,31.2Hz), 3.10(1H;dd,J=14.4,28.8Hz), 3.51(3H;s), 3.30-3.56(1H;m), 3.76(3H;s), 3.86-3.91(1H;m), 4.05-4.10(2H;m),4.32(1H;d,J=6.4Hz), 7.17-7.61 (10H;mMS(FAB, Pos.): 576 (M+1) examples 153-**N-(1S) -1-cyclohexyl methyl-2-hydroxy-3-(1-methyl-5-tetra-ZORIRU) thio propyl carbamoyl**-2, 3-dihydro-5-phenyl-1H-1, and 4-benzodiazepine-2-ON (1) 3-ethoxycarbonyl -2, 3-dihydro-2-oxo-- 5 - Phenyl-1H-benzodiazepine 2-amino benzophenone 22.0g is dissolved in pyridine 100ml, and it is diethylamino malonate. 25.0g of hydrochlorides was added and heating reflux was carried out for 7.5 hours. The solvent was distilled off, the obtained residue was dissolved in 300ml of ethyl acetate, and 300ml of water washed 3 times. The solvent was distilled off after drying an organic layer with anhydrous sodium sulfate. The obtained residue was ******ed from the acetonitrile and 4.73g of specified substance was obtained.

0061 1 H-NMR (CDCl3) : 1.30 (3 H;t, J= 8.4Hz), 4.35 (2 H;q, J= 8.4Hz) 4.60 (1 H;s),

7.06-7.63 (9 H;m), 9.60 (1 H;s) (2) 2 and 3-dihydro-2-oxo--5-phenyl **- oxo--5-phenyl-1H-benzodiazepine 1.00g** - 1H-benzodiazepine-3-yl-carbonyl hydrazide 3-ethoxycarbonyl -2, 3-dihydro - 2 It dissolved in ethanol 10ml, 1ml **of hydrazine 1 hydrates** and ethanol 10ml was added, and it stirred at the room temperature overnight. After filtering a reaction mixture, ethanol and ethyl acetate washed the obtained residue, and 0.57g of specified substance was obtained.

0062 (3) 3-**N- (1S)-1-cyclohexyl methyl-2-hydroxy-3- (1-methyl-5-tetra-ZORIRU) Thio propyl carbamoyl** -2, 3-dihydro-5-phenyl-1H-1, the 4-benzodiazepine-2-ON 2, and 3-dihydro-2-oxo--5-phenyl-1H-benzodiazepine-3-yl-carbonyl hydrazide 0.50g were dissolved in dimethyl formamide 5ml, and it cooled at -40 degrees C. 4 convention hydrogen chloride / dioxane 1.7ml, and 0.23ml of isoamyl nitrites were added to this, and it stirred for 40 minutes at -40 degrees C. a reaction mixture -78 degrees C -- cooling -- triethylamine 0.95ml -- adding -- further (1S) -1- a 534mg **of cyclohexyl methyl-2-hydroxy-3-(1-methyl-5-tetra-ZORIRU) thio propylamine hydrochlorides** , and triethylamine 0.28ml dimethyl formamide 7ml solution -- in addition, it stirred at 4 degrees C overnight. The solvent of a reaction mixture was distilled off and the obtained residue was dissolved in 50ml of ethyl acetate. Sequential washing of this was carried out by 50ml of water, 50ml of saturation sodium-hydrogencarbonate water solutions, 50ml of water, and 50ml of saturation brine. The obtained organic layer was dried with anhydrous sodium sulfate, and the solvent was distilled off. The silica gel column chromatography (eluate: ethyl acetate / n-hexane =2/1) refined residue, and the specified substance was obtained with 76% of yield (0.41g of high polar compounds, 0.30g of low polar compounds).

0063 High polar compound Rf value 0.13 (ethyl acetate / n-hexane = 2/1) 1H-NMR(CDCl3): 0.87-1.88(13H;m), 3.48(1H;dd,J=14.0,6.8Hz), 3.54(1H;d,J=5.6Hz), 3.68(1H;dd,J=34.8,14.4Hz), 3.69(1H;dd,J=34.8,14.4Hz), 3.90,3.92(3H;s), 4.02(1H;bs), 4.20-4.28,4.42-4.49(1H;m), 4.34(1H;s), 7.13-7.91(9H;m), 9.55,9.56(1H;s)MS(FAB,Pos.): 548 (M+1) low-polar compound Rf value 0.21 (ethyl acetate / n-hexane = 2/1) 1H-NMR(CDCl3): 0.87-1.97(13H;m), 3.48(1H;dd,J=14.0,6.8Hz), 3.54(1H;d,J=6.0Hz), 3.68(1H;dd,J=35.6,14.4Hz), 3.69(1H;dd,J=35.6,14.4Hz), 3.90,3.92(3H;s), 4.02,4.09(1H;bs), 4.20-4.27,4.42-4.49(1H;m), 4.33(1H;s), 7.10-7.58(8H;m), 7.90,8.27(1H;d,J=9.6Hz), 9.63 and 9.66(1 H;s) MS(FAB, Pos.): 548 (M+1) examples 16N-**(1S) -1-cyclohexyl methyl-2-hydroxy-3-(1-methyl-5-tetra-ZORIRU) thio propyl**-2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, and 4-benzodiazepine-3-carboxamide (1) By the same actuation as 3-ethoxycarbonyl -2 and the 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-benzodiazepine example 14 (1) Benzyl 2- () (3S) -2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU acetate and benzyl It is 3-ethoxycarbonyl instead of the equivalent mixture of 2-(3R) (-2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) acetate. - 2, 3-dihydro - the 2-oxo--5-phenyl-1H-benzodiazepine It used and the specified substance was obtained with 60% of yield.

0064 1 H-NMR (CDCl3) : 1.37 (3 H;t, J= 8.1Hz), 3.45 (3 H;s) 4.43 (2 H;q, J = 8/1Hz), 4.53 (1 H;s), 7.16-7.70(9 H;m) MS (FAB, Pos.) : 323 (M+1) (2) 2 and 3-dihydro-1-methyl-2-oxo-- 5 - by the same actuation as the phenyl-1H-benzodiazepine-3-yl-carbonyl hydrazide example 15 (2) 3-ethoxycarbonyl -2, 3-dihydro - It is 3-ethoxycarbonyl instead of the 2-oxo--5-phenyl-1H-benzodiazepine. - 2, 3-dihydro-1-methyl - The specified substance was obtained with 53% of yield using the 2-oxo--5-phenyl-1H-benzodiazepine.

0065 1 H-NMR (DMSO-d6) : 1.06 (3 H;t, J= 7.0Hz), 3.33 (3 H;s), 4.20 (1 H;s), 4.32 (2 H;q, J= 7.0Hz), 4.49 (2 H;bs) 7.29-7.80 (9 H;m), 9.38(1 H;bs) MS(FAB, Pos.): 309 (M+1) (3) N- **(1S)-1-cyclohexyl methyl-2-hydroxy-3- (1-methyl-5-tetra-ZORIRU) Thio propyl** by the same actuation as the -2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, and 4-benzodiazepine-3-carboxamide example 15 (2) Instead of 2 and 3-dihydro-2-oxo--5-phenyl-1H-benzodiazepine-3-yl-carbonyl hydrazide, 2 and 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-benzodiazepine-3-yl-carbonyl hydrazide It used and the specified substance was obtained with 61% of yield (0.22g of high polar compounds, 0.13g of low polar

compounds).
0066 High polar compound Rf value 0.16 (ethyl acetate / n-hexane = 2/1)
1 H-NMR (CDCl3) : 0.88-1.88 (13 H;m), 3.42 (3 H;s) 3.48 (1 H;q, J= 6.8Hz), 3.64-3.78 (2 H;m), 3.93 (3 H;s), 3.94-4.07 (2 H;m), 4.11-4.18, 4.42-4.47 (1 H;m), 4.35 (1 H;s), 7.22-7.65 (8 H;m), 8.83(1 H;d, J= 10.0Hz) MS (FAB, Pos.) : 562 (M+1) low polar compound Rf value 0.19 (ethyl acetate / n-hexane = 2/1)
1H-NMR(CDCl3): 0.88-1.03(3H;m), 1.16-1.36(5H;m), 1.52-1.55(2H;m), 1.6-1.74(3H;m), 1.88-1.96(2H;m), 3.45(3H;s), 3.48(1H;q,J=7.2Hz), 3.54-3.56(2H;m), 3.93(3H;s), 4.14-4.15(2H;m), 4.32(1H;s), 4.90(1H;d,J=6.4Hz), 7.21-7.65(8H;m), 8.22 (1H;d,J=8.8Hz)MS(FAB and Pos.: 562 (M+1) examples 17N- **(1S)-1-cyclohexyl methyl-2-hydroxy-3- (1-methyl-5-tetra-ZORIRU) thio propyl**-2-(3S) (-2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) propione amide (1) Benzyl By the same actuation as 2-(3S) (-2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) acetate example 14 (1) Benzyl 2- () (3S) -2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU acetate and benzyl 2- () instead of **of the equivalent mixture of (3R)-2, 3-dihydro-2-oxo--5-phenyl-1H-1, and 4-benzodiazepine-3-IRU acetate** -- benzyl 2- (3S) (-2 and 3-dihydro-2-oxo--5-phenyl-1H-1 --) The specified substance was obtained with 94% of yield using 4-benzodiazepine-3-IRU acetate.
0067 (2) Benzyl 2-(3S) (-2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) propionate diisopropylamine 0.22ml was dissolved in tetrahydrofuran 2ml, after cooling at -78 degrees C, 1.5Mn-butyl lithium / n-hexane 0.68ml was added, and it stirred for 15 minutes at -78 degrees C. It is benzyl to this. The 2-(3S) (-2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) acetate 0.42g tetrahydrofuran 4ml solution was added, and it stirred for 15 minutes at -78 degrees C. Iodine methyl 0.10ml was added to this, and it stirred for 30 minutes at -78 degrees C. The reaction mixture was vacated for 100ml of decinormal hydrochloric-acid water solutions, it extracted by ethyl-acetate 100mlx2, and sequential washing of the organic layer was carried out by 100ml of water, 100ml of saturation sodium-hydrogencarbonate water solutions, 100ml of water, and 100ml of saturation brine. The silica gel column chromatography (eluate: ethyl acetate / n-hexane =1/20) refined the residue which distilled off the solvent after desiccation with anhydrous sodium sulfate, and was obtained in the organic layer, and 0.21g of specified substance was obtained.
0068 1 H-NMR (CDCl3) : 1.42 (3 H;d, J= 7.1Hz), 3/40 (3 H;s), 3.60-3.93 (2 H;m), 5.16 (2 H;dd, J= 23.0, 10.6Hz), 7.17-7.65(14 H;m) MS () **EI, In** Beam: 412 (M+) (3) By the same actuation as 2-(3S) (-2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) propionic-acid example 13 (7) Benzyl 2- () (3S) -2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU acetate and benzyl 2- () instead of **of the equivalent mixture of (3R)-2, 3-dihydro-2-oxo--5-phenyl-1H-1, and 4-benzodiazepine-3-IRU acetate** -- benzyl 2- (3S) (-2 and 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1 --) The specified substance was obtained using 4-benzodiazepine-3-IRU propionate.
0069 (4) N- **(1S)-1-cyclohexyl methyl-2-hydroxy-3- (1-methyl-5-tetra-ZORIRU) By the same actuation as the thio propyl**-2-(3S) (-2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) propione amide example 13 (8) Instead of 2-(2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) acetic acid, 2-(3S) (-2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) propionic acid It used and the specified substance was obtained with 77% of yield (0.07g of high polar compounds, 0.15g of low polar compounds).
0070 High polar compound Rf value 0.05 (ethyl acetate / n-hexane = 2/1)
1H-NMR(CDCl3): 0.80-1.01(3H;m), 1.05-1.43(5H;m), 1.34(3H;d,J=7.2Hz), 1.52-1.79(6H;m), 3.08-3.18(1H;m), 3.39(3H;m), 3.41-3.55(2H;m), 3.70(1H;d,J=4.4Hz), 3.78-3.80(1H;m), 3.89(3H;s), 4.04(1H;d,J=6.8Hz), 4.09-4.14(1H;m), 7.21-7.64(8H;m), 7.98(1H;d,J=8.4HzMS (FAB, Pos.) : 590 (M+1) low polar compound Rf value 0.18 (ethyl acetate / n-hexane = 2/1)

1H-NMR(CDCl3): 0.80-0.99(3H;m), 1.09-1.42(5H;m), 1.36(3H;d,J=7.4Hz), 1.51-1.69(5H;m), 1.78(1H;d,J=12.4Hz), 3.31(1H;dd,J=9.2,7.2Hz), 3.38(3H;s), 3.44-3.55(2H;m), 3.83(1H;d,J=9.2Hz), 3.88-3.97(1H;m), 3.93(3H;s), 6.47(1H;d,J=8.8Hz), 7.19-7.63(9H;m)MS(FAB and Pos.: 590 (M+1) examples 18N- **(1S)-1-cyclohexyl methyl-2-hydroxy-3- Thio propyl**-2- (1-methyl-5-tetra-ZORIRU) () (3S) -2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, and 4-benzodiazepine-3-IRU VARERU amide (1) 2- (-2 and 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1 --) Benzyl (3S) The allyl bromide was used instead of iodine methyl by the same actuation as the 4-benzodiazepine-3-IRU-4-PENTENOETO example 17 (2), and the specified substance was obtained with 50% of yield.

0071 1 H-NMR (CDCl3) : 2.55-2.84 (2 H;m), 3.40 (3 H;s), 3.64-4.00 (2 H;m), 4.69-5.35 (2 H;m), 5.21 (2 H;s) 5.45-6.00 (1 H;m), 7.10-7.68 (14 H;m) MS (FAB, Pos.) : 439 (M+1) (2) By the same actuation as 2-(3S) (-2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) pentanoic acid example 13 (7) Benzyl 2- () (3S) -2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU acetate and benzyl 2- () instead of **of the equivalent mixture of (3R)-2, 3-dihydro-2-oxo--5-phenyl-1H-1, and 4-benzodiazepine-3-IRU acetate** -- benzyl 2- (3S) (-2 and 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1 --) The specified substance was obtained with 85% of yield using 4-benzodiazepine-3-IRU-4-PENTENOETO.

0072 MS(FAB, Pos.): 351 (M+1) (3) N- **(1S)-1-cyclohexyl methyl-2-hydroxy-3- (1-methyl-5-tetra-ZORIRU) By the same actuation as the thio propyl**-2-(3S) (-2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) VARERU amide example 13 (8) Instead of 2-(2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) acetic acid, 2-(3S) (-2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) pentanoic acid It used and the specified substance was obtained with 31% of yield.

0073 1 H-NMR (CDCl3) : 0.84-1.90 (20 H;m), 3.11-3.31 (2 H;m) and 3. -- 39 and 3.50 (3 H;s) -- 3.74-3.85 (1 H;m) and 3. -- 92 and 3.95 (3 H;s) -- 4.22-4.39 (1 H;m), 4.55-4.77 (1 H;m), 4.86 (1 H;d, J= 8.1Hz) 6.22 (1 H;d, J= 10.8Hz), 7.21-7.64 (8 H;m), 8.10 (1 H;d, J= 10.8Hz) MS(FAB, Pos.): 618 (M+1) examples 19(1)2-(benzoyl ANIRINO)-N-(t-butoxycarbonyl)-L-asparatic acid beta-benzyl ester dimethylformamide 150ml -- inside -- hydroxy benzothoria ZONIRU4.46g and dicyclohexylcarbodiimide 7.43g -- And N -(t-butoxycarbonyl)- L-asparatic acid After carrying out sequential addition of the beta-benzyl ester 10.67g, 2-amino benzophenone 5.92g was added and it agitated at the room temperature overnight. The filtrate obtained by carrying out suction filtration of the suspension solution was filled with 100ml of saturation sodium-hydrogencarbonate water solutions, and 100ml of ethyl acetate extracted. Sequential washing of the obtained organic layer was carried out with purified water and saturation brine, and it dried with sulfuric anhydride magnesium. The silica gel column chromatography (eluate; ethyl acetate / n-hexane =1/3) refined the obtained residue after solvent distilling off, and 9.02g of specified substance was obtained.

0074 1 H-NMR (CDCl3) : 1.47 (9 H;s) 3.10 (2 H;br), 4.70 (1 H;br), 5.11 (2 H;s), 5.85 (1 H;br), 6.95-7.63 (13 H;m), 8.62 (1 H;br), 11.60(1 H;br) MS(FAB): 503(M++1) (2) (3R)-3-**(benzyloxycarbonyl) methyl** -2, 3-dihydro-5-phenyl-1H-1, and 4-benzodiazepine-2-ON 2-(benzoyl ANIRINO)-N-(t-butoxycarbonyl)-L-asparatic acid After adding beta-benzyl ester 9.0g into 160ml of 4-N hydrochloric-acid-dioxane solutions and carrying out room temperature churning for 1 hour, 150ml of saturation sodium-hydrogencarbonate water solutions was added to the produced residue which carried out solvent distilling off, and 250ml of ethyl acetate extracted. Sequential washing of the organic layer was carried out with purified water and saturation brine, and it was made to dry with sulfuric anhydride magnesium. Solvent distilling off was carried out, the produced oil was filled with benzene 150ml, and heating reflux was carried out for 4 hours. After pouring out the purified water of optimum dose and rinsing in a reaction solution, crystallization was attained with little diisopropyl ether to the residue which carried out desiccation concentration of the organic layer, and was produced, this was separated, and 3.54g of specified substance was

obtained.
0075 1 H-NMR (CDCl3) : 3.32-3.45 (2 H;m), 4.20 (1 H;t, J= 7.2Hz) 5.19 (2 H;s), 7.16-7.53 (14 H;m), 8.64(1 H;br) MS(FAB): 385(M++1) IR numax(KBr) cm-1 : By the same actuation as the 1746, 1688, 1612, 1174(3) (3R)-3-**(benzyloxycarbonyl) methyl**-2, 3-dihydro-1-methyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 25 (3) 2, 3-dihydro-7-ethyl -5 - Instead of phenyl 1H-**2 and 3-thieno e 1, 4** diazepine-2-ON, (3R)-3-**(benzyloxycarbonyl) methyl**-2, 3-dihydro-5-phenyl-1H-1, and 4-benzodiazepine-2-ON It used and the specified substance was obtained with 87% of yield.
0076 1 H-NMR (CDCl3) : 3.28-3.48 (2 H;m), 3.42 (3 H;s) 4.16 (1 H;t, J= 8.0Hz), 5.15 (2 H;d, J= 2.0Hz), 7.14-7.66(14 H;m) MS () **EI, In** Beam: 398(4)2-**(3S) -2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, and 4-benzodiazepine-3-IRU**-3-phenyl It sets at -78 degrees C under a benzyl propionate ester argon gas air current. Diisopropylamine 0.34ml, 1.42ml of butyl lithium-hexane solutions included tetrahydrofuran (THF) 10ml -- inside -- (3R)-3- **(benzyloxycarbonyl) methyl** -- THF3ml containing -2, 3-dihydro-1-methyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON 0.8g was dropped, and it agitated for 15 minutes. Then, benzyl bromide 2.38ml is dropped, after carrying out room temperature churning for 1 hour, it poured into 100ml of 0.1-N hydrochloric acids, and 100ml solution of ethyl acetate, and the organic layer was dried with sulfuric anhydride magnesium. The silica gel column chromatography (eluate; benzene / ethyl-acetate =50/1) refined the residue which distilled off the solvent and was produced, and 0.35g of specified substance was obtained.
0077 1 H-NMR (CDCl3) : 2.85-3.15 (2 H;m), 3.38 (3 H;s), 3.80-4.02 (2 H;m), 5.00 (2 H;q.J=12.6Hz), 6.98-7.53(19 H;m) MS () **EI, In** Beam: 489 (5) 2- **(3S) -2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU**-3-phenyl propionic-acid 2-**(3S)-2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU**-3-phenyl benzyl propionate ester 0.3g -- ethanol 15ml -- the amount addition of catalysts of the palladium carbon was carried out 10% at the solution added to inside, and it heated at 50 degrees C overnight. The catalyst was filtered out by SERAIDO after the reaction, the obtained filtrate was condensed, and 0.24g of specified substance was obtained.
0078 1 H-NMR (CDCl3) : 3.20-3.84 (4 H;m), 3.44 (3 H;s) 5.10 (1 H;br), 7.26-7.66(14 H;m) MS(FAB): 399 (M++1) (6) N- **(1S)-1-cyclohexyl methyl-2-hydroxy-3- Thio propyl**-2-**(1-methyl-5-tetra-ZORIRU) (3S) -2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU**-3-phenyl propione amide 2-**(3S)-2, 3-dihydro-1-methyl-2-oxo--5-phenyl-1H-1, 0.2g of 4-benzodiazepine-3-IRU**-3-phenyl propionic acids (1S), -1 - 0.33g of cyclohexyl methyl-2-hydroxy-3-**(1-methyl-5-tetrapod ZORIRU) thio** propylamine hydrochlorides is melted to dimethylformamide 5ml Naka. Bottom diphenyl phosphoric-acid azide of ice-cooling 0.13ml and triethylamine 0.08ml were added, and it agitated at the room temperature overnight. After it filled the reaction solution with 50ml of saturation sodium-hydrogencarbonate water solutions and 50ml of ethyl acetate extracted, 50ml of purified water and 50ml of saturation brine washed. After drying an organic layer with sulfuric anhydride magnesium, the silica gel column chromatography (eluate; ethyl acetate / hexane =1/1) refined the residue produced by solvent distilling off, and 0.03g of specified substance was obtained.
0079 MS(FAB): 666 (M++1) examples toluene 40ml cooled by 20(1) 2, 3-dihydro-1-ethyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON 0 degree C -- Alliquat336 of the amount of catalysts, and 1.2ml of ethyl iodides to inside Sequential addition of the 15ml **of 50% sodium-hydroxide water solutions** , 2, 3-dihydro-5-phenyl-1H-1, and 4-benzodiazepine-2-ON 2.36g was carried out, and room temperature churning was carried out for 4 hours. After pouring out 50ml of purified water, and 50ml of ethyl acetate and separating liquids, saturation brine washed the obtained organic layer and it was made to dry with sulfuric anhydride magnesium after a reaction. The silica gel column chromatography (eluate; chloroform) refined the residue produced by solvent distilling off, and 1.27g of specified substance was obtained.
0080 1 H-NMR (CDCl3) : 1.13 (3 H;t, J= 6.0Hz), 4.27 (2 H;q, J= 6.0Hz) 3.64-4.45 (2

H;m), 7.12-7.68(9 H;m) MS (GC): 264(M+) IR numax(KBr) cm-1 : 2966, 2952, 1674, 1610 (2) -- the bottom of a 2, 3-dihydro-1-ethyl-3-OKISHIMIDO-5-phenyl-1H-1, and 4-benzodiazepine-2-on-argon air current -- toluene 30ml -- to inside 2, 3-dihydro-1-ethyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON 1.83g It added, t-butoxy potassium 2.0g was added in -20 degrees C, and it agitated for 10 minutes. Then, after dropping 1.1ml of amyl nitrites and agitating for 1 hour, the cooled mixed liquor (60ml of purified water, 4ml of acetic acids, 60ml of ethyl acetate) was poured out. The organic layer was isolated preparatively and 1.79g of specified substance was obtained by distilling off a solvent after desiccation with sulfuric anhydride magnesium.

0081 1 H-NMR (CDCl3) : 1.13 (3 H;t, J= 10.8Hz), 4.08 (2 H;br) 7.10-7.86 (9 H;m), 8.12(1 H;m) MS () **EI, In** Beam: 293(M+) IR numax(KBr) cm-1 : 3300, 1684, 1610, 698(3)3-amino -2, 3-dihydro-1-ethyl-5-phenyl-1H-1, 4-benzodiazepine-2-ON 2, 3-dihydro-1-ethyl-3-OKISHIMIDO-5-phenyl-1H-1, and 4-benzodiazepine-2-ON 1.73g After melting to methanol 20ml Naka and adding 0.43g of ruthenium carbon 5%, it agitated under hydrogen gas existence overnight under the pressurization conditions of 70-degree-C 4.2 atmospheric pressures. The filtrate which filtered out the catalyst and was obtained was condensed, the silica gel column chromatography (eluate; chloroform) refined the produced residue, and 0.83g of specified substance was obtained.

0082 1 H-NMR (CDCl3) : 1.66-1.26 (3 H;m), 3.67-4.43 (3 H;m), 7.10-7.67(9 H;m) MS () **EI, In** Beam: 279 (M+) (4) by the same actuation as the (3R)-3-**3-(1S) -1-cyclohexyl methyl-2-hydroxy-2-isopropyl oxycarbonyl ethyl ureido**-1, 3-dihydro-1-ethyl-5-phenyl-2H-1, and 4-benzodiazepine-2-ON example 1 The (3R)-3-amino -2, 3-dihydro-1-methyl-5-phenyl-1H-1 and 4-benzodiazepine-2-ON and (1S) -1 - Instead of a cyclohexyl methyl-2-hydroxy-3-**(1-methyl-5-tetra-ZORIRU) thio** propylamine hydrochloride, 3-amino -2, The specified substance was obtained with 51% of yield using 3-dihydro-1-ethyl-5-phenyl-1H-1 and 4-benzodiazepine-2-ON and a 3-amino-(3S)-3-cyclohexyl methyl-2-hydroxy propionic-acid isopropyl ester hydrochloride.

0083 MS (FAB) : 549(M++1) IR numax(KBr) cm-1 : 3412, 2940, 1738, 1680, 1106 examples 21 (1)

Allyl compound bromide was used instead of the ethyl iodide by the same actuation as the 1-allyl compound -2, 3-dihydro-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 20 (2), and the specified substance was obtained with 94% of yield.

0084 1H-NMR(CDCl3): -- 4.36 (2 H;q, J= 10.8Hz), 4.58 (2 H;q, J= 16.2Hz), 5.08-5.24 (2 H;m), 5.76-5.96 (1 H;m), and 7.12-7.68(9 H;m) MS (GC): 276(M+) IR numax(KBr) cm-1 : 1682, 1612, and 786 examples 21 (2)

By the same actuation as the 1-allyl compound -2, 3-dihydro-3-OKISHIMIDO-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 20 (2) 1-allyl compound -2, 3-dihydro-5-phenyl-1H-1, and 4-benzodiazepine-2-ON was used instead of 2, 3-JIBIDORO-1-ethyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON, and the specified substance was obtained with 25% of yield.

0085 1 H-NMR (CDCl3) : 1.67 (1 H;br), 4.62 (2 H;br), 5.13-5.30 (2 H;m), 5.78-6.00 (1 H;m), 7.14-8.90(9 H;m) MS (EI, In Beam) : 305(M+) IR numax(KBr) cm-1 : 3300, 1684, 1644, 1610, 696 examples 21 (3)

By the same actuation as the 3-amino -2, 3-dihydro-5-phenyl-1-propyl-1H-1, and 4-benzodiazepine-2-ON example 20 (3) Instead of 2, 3-JIBIDORO-1-ethyl-3-OKISHIMIDO-5-phenyl-1H-1, and 4-benzodiazepine-2-ON, 1-allyl compound -2, 3-dihydro-3-OKISHIMIDO-5-phenyl-1H-1, and 4-benzodiazepine-2-ON It used and the specified substance was obtained with 57% of yield.

0086 1 H-NMR (CDCl3) : 0.96 (3 H;t, J= 10.8Hz), 1.35- 1.69 (2 H;m), 2.42 (2 H;br), and 3.56-3.74 (1 H;m) -- 4.16- 4.44 (1 H;m), 4.50 (1 H;br), and 7.16-7.70(9 H;m) MS(EI, In Beam): 293(M+) IR numax(KBr) cm-1 : 3408, 2980, 1680, and 1606 examples 21 (4)

(3R)-3-**3- (1S)-1-cyclohexyl methyl-2-hydroxy-2-(isopropyl oxycarbonyl) ethyl ureido** by the same actuation as the -2, 3-dihydro-5-phenyl-1-propyl-1H-1, and 4-benzodiazepine-2-ON example 1 The (3R)-3-amino -2, 3-dihydro-1-methyl - 5-phenyl-1H-

benzodiazepine-2-ON and (1S) -1 - Instead of a cyclohexyl methyl-2-hydroxy-3-**(1-methyl-5-tetra-ZORIRU) thio** propylamine hydrochloride, 3-amino -2, 3-dihydro-5-phenyl - The specified substance was obtained with 24% of yield using 1-propyl-1H-benzodiazepine-2-ON and a 3-amino-(3S)-3-cyclohexyl methyl-2-hydroxy propionic-acid isopropyl ester hydrochloride.
0087 MS(FAB): FAB 563(M++1) IR numax(KBr) cm-1 : 3412, 2984, 1734, 1674 examples 22 (1)
Iodation isopropyl was used instead of the ethyl iodide by the same actuation as the 2, 3-dihydro-1-isopropyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 20 (1), and the specified substance was obtained with 39% of yield.
0088 1 H-NMR (CDCl3) : 1.24 (3 H;d, J= 7.2Hz), 3.69 (1 H;d, J= 10.4Hz), 4.48-4.78 (3H, m), 7.20-7.69(9 H;m) MS (GC): 278(M+) IR numax(KBr) cm-1 : 2988, 1674, 706 examples 22 (2)
By the same actuation as the 2, 3-dihydro-1-isopropyl-3-OKISHIMIDO-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 20 (2) 2, 3-dihydro-1-isopropyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON was used instead of 2, 3-dihydro-1-ethyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON, and the specified substance was obtained with 79% of yield.
0089 1 H-NMR(CDCl3): 3272, 3072, 1654, 1610, 698 examples 22 (3) 1.33 (3 H;d, J= 7.9Hz), 1.57 (3 H;d, J= 7.6Hz), 4.49 (1 H:h, J= 7.6Hz), 7.23-7.86 (9 H;m), 10.68(1H, s) MS (EI, In Beam) : 307(M+) IR numax(KBr) cm-1 :
By the same actuation as the 3-amino -2, 3-dihydro-1-isopropyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 20 (3) Instead of 2, 3-dihydro-1-ethyl-3-OKISHIMIDO-5-phenyl-1H-1, and 4-benzodiazepine-2-ON, 2, 3-dihydro-1-isopropyl-3-OKISHIMIDO-5-phenyl-1H-1, and 4-benzodiazepine-2-ON It used and the specified substance was obtained with 28% of yield.
0090 1 H-NMR (CDCl3) : 1.25 (3 H;d, J= 7.6Hz), 1.50 (3 H;d, J= 7.6Hz), 2.56 (2 H;br), 4.44 (1 H;s), 4.59 (1 H;h, J= 7.6Hz), 7.15-7.69(9 H;m) MS (EI, In Beam) : 293 (M+) example 22 (4)
(3R)-3-**3- (1S)-1-cyclohexyl methyl-2-hydroxy-2-(isopropyl oxycarbonyl) ethyl ureido** by the same actuation as the -2, 3-dihydro-1-isopropyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 1 The (3R)-3-amino -2, 3-dihydro-1-methyl-5-phenyl-1H-1 and 4-benzodiazepine-2-ON and (1S) -1 - Instead of a cyclohexyl methyl-2-hydroxy-3-**(1-methyl-5-tetra-ZORIRU) thio** propylamine hydrochloride, 3-amino -2, The specified substance was obtained with 10% of yield using 3-dihydro-1-isopropyl-5-phenyl-1H-1 and 4-benzodiazepine-2-ON and a 3-amino-(3S)-3-cyclohexyl methyl-2-hydroxy propionic-acid isopropyl ester hydrochloride.
0091 MS(m/z): FAB 563(M++1) IR numax(KBr) cm-1 : 3416, 2992, 1736, 1676 examples 23 (1)
Benzyl bromide was used instead of the ethyl iodide by the same actuation as the 1-benzyl -2, 3-dihydro-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 20 (2), and the specified substance was obtained with 94% of yield.
0092 1 H-NMR (CDCl3) : 4.37 (2 H;q, J= 10Hz), 5.22 (2 H;q, J= 16Hz), 6.92-7.52(14 H;m) MS (EI, In Beam) : 326(M+) IR numax(KBr) cm-1 : 3456, 1674, 754, 702 examples 23 (2)
By the same actuation as the 1-benzyl -2, 3-dihydro-3-OKISHIMIDO-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 20 (2) 1-benzyl -2, 3-dihydro-5-phenyl-1H-1, and 4-benzodiazepine-2-ON was used instead of 2, 3-dihydro-1-ethyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON, and the specified substance was obtained with 75% of yield.
0093 1 H-NMR (CDCl3) : 4.96 (1 H;br), 5.58 (1 H;br), 5.48-5.76 (1 H;m), 6.94-7.31 (14 H;m), 8.04(1 H;br) MS (EI, In Beam) : 355(M+) IR numax(KBr) cm-1 : 3328, 1682, 1608, 698 examples 23 (3)
By the same actuation as the 3-amino-1-benzyl -2, 3-dihydro-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 20 (3) Instead of 2, 3-dihydro-1-ethyl-3-OKISHIMIDO-5-phenyl-1H-1, and 4-benzodiazepine-2-ON, 1-benzyl -2, 3-dihydro-3-OKISHIMIDO-5-phenyl-

1H-1, and 4-benzodiazepine-2-ON It used and the specified substance was obtained with 36% of yield.
0094 1 H-NMR (CDCl3) : 2.32 (2 H;br), 4.61 (1 H;br), 5.26 (2 H;q, J= 16.2Hz), 6.95-7.54(15 H;m) MS (FAB) : 342(M++1) IR numax(KBr) cm-1 : 3412, 1672, 1608, 700 examples 23 (4)
(3R)-3-**3- (1S)-1-cyclohexyl methyl -2 - by the same actuation as the hydroxy-2-(isopropyl oxycarbonyl) ethyl ureido**-1-benzyl -2, 3-dihydro-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 1 The (3R)-3-amino -2, 3-dihydro-1-methyl-5-phenyl-1H-1 and 4-benzodiazepine-2-ON and (1S) -1 - Instead of a cyclohexyl methyl-2-hydroxy-3-**(1-methyl-5-tetra-ZORIRU) thio** propylamine hydrochloride, 3-amino-1-benzyl -2, 3-dihydro-5-phenyl-1H-1 and 4-benzodiazepine-2-ON and 3-amino-(3S)-3-cyclohexyl methyl-2-hydroxy propionic acid The specified substance was obtained with 23% of yield using the isopropyl ester hydrochloride.
0095 MS (m/z) : 611(M++1) IR numax(KBr) cm-1 : 3412, 2936, 1736, 1666, 698 examples 24 (1)
2-**(2-BUROMO acetyl) amino**-5 - Chlorobenzo phenon 2-amino-5-chlorobenzo phenon 4.63g was added into 2ml mixture of dichloromethane 20ml purified water, 8ml of dichloromethane solutions which contain promo acetyl bromide 2ml in -10 degrees C was dropped, and room temperature churning was carried out for 8 hours. After drying the organic layer washed in cold water and obtained by 40ml of purified water with sulfuric anhydride magnesium, the residue produced by solvent distilling off was cooled, crystallization was attained in the hexane, and 6.04g of specified substance was obtained.
0096 1 H-NMR (CDCl3) : 4.02 (2 H;s), 7.41-7.80 (7 H;m), 8.52-8.63(1 H;m) MS (EI, In Beam) : 352(M+) IR numax(KBr) cm-1 : 3240, 1688, 1636 examples 24 (2)
7-chloro -2 and the 3-dihydro-5-phenyl -1 -- H-1 and 4-benzoazepine-2-ON 2-**(2-BUROMO acetyl) amino**-5-chlorobenzo phenon 5.92g -- methanol 100ml -- it melted to inside, and it agitated, blowing ammonia gas under cooling at -10 degrees C. 2 hours after The reaction solution was returned to the room temperature and heating reflux was carried out for 3 hours. 3.15g of specified substance was obtained by separating the crystal which added cooling purified water to the residue obtained by distilling off a solvent, and was produced.
0097 1 H-NMR (DMSO-d6) : 4.17 (2 H;br), 7.20-7.71 (8 H;m), 10.65(1 H;br) MS (EI, In Beam) : 270(M+) IR numax(KBr) cm-1 : 3200, 2968, 1686 examples 24 (3)
By the same actuation as the 7-chloro -2, 3-dihydro-1-methyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 20 (1) 7-chloro -2, 3-dihydro-5-phenyl-1H-1, and 4-benzodiazepine-2-ON and a methyl iodide were used instead of 2, 3-dihydro-5-phenyl-1H-1, and 4-benzodiazepine-2-ON and an ethyl iodide, and the specified substance was obtained with 90% of yield.
0098 1 H-NMR (CDCl3) : 3.40 (3 H;s), 3.78 (1 H;d, J= 10.8Hz), 4.85 (1 H;d, J= 10.8Hz), 7.25-7.64(8 H;m) MS (EI, In Beam) : 284(M+) IR numax(KBr) cm-1 : 1684, 1614, 1486, 700 examples 24 (4)
By the same actuation as the 7-chloro -2, 3-dihydro-1-methyl-3-OKISHIMIDO-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 20 (2) 7-chloro -2, 3-dihydro-1-methyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON was used instead of 2, 3-dihydro-1-ethyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON, and the specified substance was obtained with 98% of yield.
0099 1 H-NMR (CDCl3) : 3.44 (3 H;s), 7.22-7.88(9 H;m) MS (EI, In Beam) : 313(M+) IR numax(KBr) cm-1 : 3340, 2972, 1682, 1614, 698 examples 24 (5)
By the same actuation as the 3-amino-7-chloro -2, 3-dihydro-1-methyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 20 (3) Instead of 2, 3-dihydro-1-ethyl-3-OKISHIMIDO-5-phenyl-1H-1, and 4-benzodiazepine-2-ON, 7-chloro -2, 3-dihydro-1-methyl-3-OKISHIMIDO-5-phenyl-1H-1, and 4-benzodiazepine-2-ON It used and the specified substance was obtained with 41% of yield.
0100 1 H-NMR (CDCl3) : 3.44 (3 H;s), 4.25 (1 H;br), 7.27-7.65(8 H;m) MS (GC): 299(M+) IR numax(KBr) cm-1 : 3400, 1686, 1600, 700 examples 24 (6)

(3R)-3-**3- (1S)-1-cyclohexyl methyl -2 - by the same actuation as the hydroxy-2-(isopropyl oxycarbonyl) ethyl ureido**-7-chloro -2, 3-dihydro-1-methyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON example 1 The (3R)-3-amino -2, Instead of 3-dihydro-1-methyl-5-phenyl-1H-1 and 4-benzodiazepine-2-ON and (1S) a -1-cyclohexyl methyl-2-hydroxy-3-**(1-methyl-5-tetra-ZORIRU) thio** FUROPIRU amine hydrochloride, 3-amino-7-chloro -2, 3-dihydro-1-methyl-5-phenyl-1H-1 and 4-benzodiazepine-2-ON and 3-amino-(3S)-3-cyclohexyl methyl-2-hydroxy propionic acid The specified substance was obtained with 54% of yield using the isopropyl hydrochloride.
0101 MS (FAB) : 569(M++1) IR numax(KBr) cm-1 : 3410, 2936, 2856, 1740, 1680
examples 25 (1)
The 2-amino-3-benzoyl-5-ethyl thiophene was used instead of 2-amino-5-chlorobenzo FENONN by the same actuation as the 3-benzoyl-2-**(2-BUROMO acetyl) amino**-5-ethyl thiophene example 24 (1), and the specified substance was obtained with 94% of yield.
0102 1 H-NMR (CDCl3) : 1.29 (3 H;t, J = 7 or 2Hz), 2.76 (2 H;q, J = 7 or 2Hz), 4.11 (2 H;s), 6.80-6.83 (1 H;m), 7.41-7.80 (5 H;m), 12.71(1 H;br) MS (EI, In Beam) : 352(M+) IR numax(KBr) cm-1 : 3200, 1680, 1618, 1534 examples 25 (2)
2, 3-dihydro-7-ethyl-5-phenyl - It applies to the process of the 1H-**2 and 3-thieno e 1, 4** diazepine-2-ON example 24 (2) correspondingly. Instead of 2-**(2-BUROMO acetyl) amino**-5-chlorobenzo phenon a 3-benzoyl-5-ethyl thiophene After using and blowing the bottom (-10 degrees C) ammonia gas of low temperature over 2 hours, it ****(ed) overnight, and the specified substance was obtained with 15% of yield by performing after treatment by the same actuation.
0103 1 H-NMR (CDCl3) : 1.20 (3 H;t, J= 7.2Hz), 2.74 (2 H;q, J= 7.2Hz), 4.21 (2 H;s), 6.52-6.54 (1 H;m), 7.36-7.65 (5 H;m), 11.16(1 H;br) MS (EI, In Beam) : 270(M+) IR numax(KBr) cm-1 : 3080, 2848, 1690, 1496 examples 25 (3)
Dimethylformamide 15ml is added to 2 and 0.24g of 3-dihydro-7-ethyl-1-methyl-5-phenyl-1H-**2 and 3-thieno e 1, 4** diazepine-2-ON 60% sodium hydride. After suspending under ice-cooling, 2 and 3-dihydro-7-ethyl-5-phenyl-1H-**2 and 3-thieno e 1, 4** diazepine-2-ON 1.35g were added, and it ****(ed) for 15 minutes. Then, after dropping and carrying out room temperature **** of the 0.37ml of the methyl iodides for 4 hours, 200ml of purified water was poured out and 100ml of ethyl acetate extracted twice. After saturation brine's having washed the organic layer and making it dry with sulfuric anhydride magnesium, the silica gel column chromatography (eluate; ethyl acetate / hexane =1/1) refined the residue which may have been condensed, and 0.93g of specified substance was obtained.
0104 1 H-NMR (CDCl3) : 1.29 (3 H;t, J= 7.6Hz), 2.79 (2 H;q, J= 7.6Hz), 3.45 (3 H;s), 4.41 (1 H;br), 6.49-6.52 (1 H;m), 7.35-7.73(5H, m) MS (FAB) : 285 (M+) example 25 (4)
2 3-dihydro-7-ethyl-1-methyl-3-OKISHIMIDO-5-phenyl - by the same actuation as the 1H-**2 and 3-thieno e 1, 4** diazepine-2-ON example 20 (2) Instead of 2, 3-dihydro-1-ethyl-5-phenyl-1H-1, and 4-benzodiazepine-2-ON, 2 and 3-dihydro-7-ethyl-1-methyl-5-phenyl-1H-**2 and 3-thieno e 1, 4** diazepine-2-ON It used and the specified substance was obtained with 51% of yield.
0105 1H-NMR(CDCl3): 1.29(3H;t,J=7.2Hz),2.77(2H;q,J=7.2Hz),3.54(3H;s),6.53-6.55(1H;m),7.38-7.91(5H;m
MS(EI,In Beam): 313(M+)
Example 25 (5)
The 3-amino -2, 3-dihydro-7-ethyl-1-methyl-5-phenyl - by the same actuation as the 1H-**2 and 3-thieno e 1, 4** diazepine-2-ON example 20 (3) Instead of 2, 3-dihydro-1-ethyl-3-OKISHIMIDO-5-phenyl-1H-1, and 4-benzodiazepine-2-ON, 2 and 3-dihydro-7-ethyl-1-methyl-3-OKISHIMIDO-5-phenyl-1H-**2 and 3-thieno e 1, 4** diazepine-2-ON It used and the specified substance was obtained with 56% of yield.
0106 1H-NMR(CDCl3):
1.30(3H;t,J=7.6Hz),2.40(2H;br),2.80(2H;q,J=7.6Hz),3.50(3H;s),4.12(1H;q,J=7.2Hz),6.53(1H;br),7.39-7.74(5H;m)

MS(EI,In Beam): 299(M+)
Example 25 (6)
(3R)-3-**3- (1S) -1-cyclohexyl methyl-2-hydroxy-2- (Isopropyl oxycarbonyl) ethyl ureido** by the same actuation as the -2, 3-dihydro-7-ethyl-1-methyl-5-phenyl-1H-1, and 4-**2 and 3-thieno e** diazepine-2-ON example 1 The (3R)-3-amino -2, Instead of 3-dihydro-1-methyl-5-phenyl-1H-1 and 4-benzodiazepine-2-ON and (1S) a -1-cyclohexyl methyl-2-hydroxy-3-**(1-methyl-5-tetra-ZORIRU) thio** FUROPIRU amine hydrochloride, the 3-amino -1, 3-dihydro-7-ethyl-1-methyl-5-phenyl-1H-**2 and 3-thieno e 1, 4** diazepine-2-ON and a 3-amino-(3S)-3-cyclohexyl methyl-2-hydroxy propionic-acid isopropyl ester hydrochloride It used and the specified substance was obtained with 42% of yield.
0107 MS (FAB) : 569(M+) IR numax(KBr) cm-1 : 3416, 2940, 1688, and 1550 examples 261- **(1S)-1-cyclohexyl methyl-2-hydroxy-3-(1-methyl-5-tetra-ZORIRU) thio propyl**-3-**2, 3-dihydro-1-methyl-2-oxo--5-(p-tolyl)-1H-1, and 4-benzodiazepine-3-IRU** urea (1 --) 2-(2-BUROMO acetyl) amino-4 '- methyl benzophenone 2-amino -4'-methyl benzophenone 21.1g was dissolved in 130ml of methylene chlorides, and 10ml of water, and it cooled at -10 degrees C. 2-BUROMO acetyl star's picture 10ml 30ml solution of methylene chlorides was added to this, and it stirred at the room temperature for 5 hours. 200ml of water was added to the reaction mixture, and it extracted by methylene chloride 100mlx2. The organic layer was dried with anhydrous sodium sulfate, and the solvent was distilled off. The obtained residue was washed by n-hexane 100ml, and 30.6g of specified substance was obtained.
0108 1 H-NMR (CDCl3) : 2.46 (3 H;s) 4.03 (2 H;s), 7.16 (1 H;t, J= 8.1Hz) 7.31 (2 H;d, J= 8.1Hz), 7.58-7.65 (2 H;m), 7.66 (2 H;d, J= 8.1Hz), 8.59(1 H;d, J= 8.1Hz) MS () **EI, In** Beam: 333 and 331 (2) 2 3-dihydro-5-(4-methylphenyl)-2-oxo-- 1 (H) - Benzodiazepine 2-(2-BUROMO acetyl) amino-4'-methyl benzophenone 3.50g was suspended in methanol 60ml, and it cooled at -10 degrees C. After blowing ammonia gas into it until insoluble matter melted into this, it was stirred at the room temperature to it for 4 hours. It condensed, after carrying out the heating reflux of the reaction mixture for 2 hours. The obtained residue was warmed at 40 degrees C, 10ml of water was added, and it stirred at the room temperature overnight. The depositing crystal was separated, it washed by the methanol / water =1/1, and 2.54g of specified substance was obtained.
0109 1 H-NMR (DMSO-d6) : 2.38 (3 H;s) 4.14 (2 H;s), 7.02-7.59 (8 H;m), 10.42(1 H;s) MS (EI, In Beam) : 249 (M-1) (3) 2 and 3-dihydro-1-methyl-5-(4-methylphenyl)-2-oxo--1(H)-benzodiazepine toluene 18ml are cooled at 0 degree C. To this, ant KUATTO 336 1ml, iodine methyl 0.66ml, 2, a 3-dihydro-5-(4-methylphenyl)-2-oxo--1(H)-benzodiazepine 2.42g toluene 30ml solution, 18ml of sodium-hydroxide water solutions was added one by one 50%, and it stirred at the room temperature for 5 hours. The reaction mixture was extracted by toluene 50mlx2, and 50ml of water washed the obtained organic layer. The residue which distilled off the solvent after desiccation with anhydrous sodium sulfate, and was obtained in the organic layer was crystallized from the ether / n-hexane, and 2.05g of specified substance was obtained.
0110 1 H-NMR (CDCl3) : 2.39 (3 H;s) 3.41 (3 H;s), 3.76 (1 H;d, J= 9.9Hz) 4.79 (1 H;d, J= 10.8Hz), 7.15-7.56(8 H;m) MS (GC): 263 (M-1) (4) 2 and 3-dihydro-1-methyl-5-(4-methylphenyl)- the 3-OKISHIMIDO-2-oxo--1(H)-benzodiazepine 2 and 3-dihydro-1-methyl-5-(4-methylphenyl)- 2-oxo--1(H)-benzodiazepine 2.00g It dissolved in toluene 40ml and cooled at -20 degrees C. After adding potassium t-butoxide 2.24g to this and stirring for 15 minutes at -20 degrees C, 1.26ml of isoamyl nitrites was added and it stirred for 30 minutes at 0 degree C. The reaction mixture was vacated for 80ml of 4ml-ethyl acetate of 80ml-acetic acids of iced water, and it extracted by ethyl-acetate 80mlx2. The organic layer was dried with anhydrous sodium sulfate, the residue obtained by distilling off a solvent was crystallized from toluene / n-hexane, and 1.59g of specified substance was obtained.
0111 1 H-NMR (CDCl3) : 2.42 (3 H;s) 3.46 (3 H;s), 7.19-7.76(8 H;m) MS () **EI, In** Beam: 293 (M+) (5) The 3-amino -2, the 3-dihydro-1-methyl-5-(4-methylphenyl)-2-oxo--1(H)-

benzodiazepine 2, 3-dihydro-1-methyl-5-(4-methylphenyl)-3 - OKISHIMIDO-2-oxo--1(H)-benzodiazepine 0.59g It dissolved in methanol 10ml, a ruthenium / 0.15g of carbon were added, and it stirred at 70 degrees C under hydrogen (40psi) overnight. After carrying out cerite filtration of the reaction mixture, the solvent was distilled off and 0.57g of specified substance was obtained.

0112 1 H-NMR (CDCl3) : 2.39 (3 H;s) 3.46 (3 H;s), 7.15-7.57(8 H;m) MS () **EI, In** Beam: 279 (M+) (6) 1- **(1S)-1-cyclohexyl methyl-2-hydroxy-3- (1-methyl-5-tetra-ZORIRU) By the same actuation as the thio propyl**-3-**2, 3-dihydro-1-methyl-2-oxo--5-(p-tolyl)-1H-1, and 4-benzodiazepine-3-IRU** urea example 11 The 3-amino -2 and the 3-dihydro-1-methyl-5-(4-methylphenyl)-2-oxo--1(H)-benzodiazepine are used instead of 3-aminomethyl -2, 3-dihydro-5-phenyl-1H-1, and 4-benzodiazepine-2-ON. The specified substance was obtained with 81% of yield (0.48g of high polar compounds, 0.47g of low polar compounds).

0113 High polar compound Rf value 0.13 (ethyl acetate / n-hexane = 2/1)
1H-NMR(CDCl3): 0.78-0.90(3H;m), 1.08-1.34(5H;m), 1.43-1.49(1H;m), 1.58-1.69(3H;m), 1.75(1H;d,J=12.8Hz), 2.37(3H;s), 3.40-3.51(2H;m), 3.47(3H;s), 3.88(3H;s), 3.89-3.93(1H;m), 3.96-4.00(1H;m), 4.47(1h;s), 5.44(1H;d,J=8.4Hz), 5.58(1H;d,J=9.2Hz), 6.81(1H;d, J= 8.4Hz, 7.17-7.23 (2 H;m), 7.34-7.40 (2 H;m), 7.50 (2 H;d, J= 8.4Hz), 7.54-7.59(1 H;m) MS (FAB, Pos.) : 591 (M+1) low polar compound Rf value 0.26 (ethyl acetate / n-hexane = 2/1)
1H-NMR(CDCl3): 0.77-0.90(3H;m), 1.06-1.42(5H;m), 1.46-1.73(5H;m), 2.37(3H;s), 3.38-3.52(2H;m), 3.47(3H;s), 3.51-3.79(1H;m), 3.88-3.93(1H;m), 3.91(3H;s), 4.52-4.56(1H;m), 5.46(1H;d,J=8.8Hz), 5.62(1H;d,J=8.8Hz), 6.81(1H;d,J=8.4Hz), 7.16(1H;d,J=8.0Hz),7.23 (1 H;t, J= 7.6Hz), 7.34-7.39 (2 H;m), 7.48 (2 H;d, J= 8.0Hz), 7.55-7.59(1 H;m) MS(FAB, Pos.): 591 (M+1) examples 27N- **(1S)-1-cyclohexyl methyl-2-hydroxy-3-(1-methyl-5-tetra-ZORIRU) thio propyl**-2-(3S) (-2, 3-dihydro - 1, 5-dimethyl-2-oxo--1H-1, 4-benzodiazepine-3-IRU) acetamido (1 --) N-t-butyloxy carbonyl-L-asparatic acid 2-amino acetophenone was used instead of 2-amino benzophenone by the same actuation as the alpha-2-benzophenone amide beta-benzyl ester example 13 (1), and the specified substance was obtained with 65% of yield.

0114 1H-NMR(CDCl3): 1.52(9H;s), 2.63(3H;s), 2.96, (2H;dd,J=42.8,4.6Hz), 3.16(1H;dd,J=43.1,4.6Hz), 4.67(1H;t,J=4.6Hz), 4.77(1H;t,J=4.6Hz), 5.11,5.13(2H;s), 5.74,5.84(1H;bs), 7.16,7.17(1H;q,J=7.7Hz), 7.31(5H;s), 7.54,7.56(1H;t,J=8.8Hz), 7.87,7.89(1H;d,J=7.9Hz, 8. -- 72 and 8.73 (1 H;d, J= 8.4Hz) -- 12.42(1 H;s) MS(FAB, Pos.): 440 (M+1) (2) Benzyl 2-(2, 3-dihydro-5-methyl - 2-oxo--1(H)-benzodiazepine-3-IRU) acetate N-t-butyloxy carbonyl-L-asparatic acid alpha-2-benzophenone amide beta-benzyl ester 4.40g It dissolved in 4 convention hydrogen chloride / dioxane 100ml, and stirred at the room temperature for 1 hour. The solvent was distilled off, 100ml of saturation sodium-hydrogencarbonate water solutions was added to residue, and it extracted by ethyl-acetate 100mlx2. Sequential washing of the organic layer was carried out by 100ml of water, and 100ml of saturation brine, and the solvent was distilled off after drying with anhydrous sodium sulfate.

0115 The obtained residue was dissolved in benzene 30ml, the para toluenesulfonic acid of the amount of catalysts was added, and heating reflux was carried out for 4 hours. 100ml of saturation sodium-hydrogencarbonate water solutions was added to the reaction mixture, and it extracted by ethyl-acetate 100mlx2. Sequential washing of the organic layer was carried out by 100ml of water, and 100ml of saturation brine, after drying with anhydrous sodium sulfate, the solvent was distilled off, and 2.92g of specified substance was obtained.

0116 1H-NMR(CDCl3): 2. -- 40 and 2.43 (3 H;s) -- 3. -- 20, 3.27 (2 H;q, J= 16.0Hz), and 4.02 (1 H;t, J= 18.0Hz) -- 5.13 (2 H;s), 6.99-7.58 (4 H;m), 7.31 (5 H;s), 9.07(1 H;s) MS (GC): 322 (M+) (3) Benzyl By the same actuation as 2-(2, 3-dihydro - 1, 5-dimethyl - 2-oxo--1(H)-benzodiazepine-3-IRU) acetate example 14 (1) Benzyl 2- () (3S) -2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU acetate and benzyl 2- (3R) It is benzyl

instead of the equivalent mixture of acetate (-2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU). 2-(2, 3-dihydro-5-methyl - 2-oxo--1(H)-benzodiazepine-3-IRU) acetate It used and the specified substance was obtained with 68% of yield.
0117 1H-NMR(CDCl3): 2. -- 43 and 2.45 (3 H;s) -- 3. -- 21 and 3.28 (2 H;dd, J= 33.2, 17.0Hz) -- 3.38 (3 H;s) 3.96 (1 H;d, J= 7.6Hz), 5.12 (2 H;s) 7.15-7.59 (4 H;m), 7.32(5 H;s) MS (GC): 336 (M+) (4) 2-(2, 3-dihydro - 1, 5-dimethyl - 2-oxo--1(H)-benzodiazepine-3-IRU) benzyl acetate 2-(2, 3-dihydro - 1, 5-dimethyl - 2-oxo--1(H)-benzodiazepine-3-IRU) acetate 0.34g It dissolved in methanol 10ml, the palladium/carbon of the amount of catalysts were added, and it stirred at the bottom room temperature of ordinary pressure hydrogen for 1.5 hours. After carrying out cerite filtration of the reaction mixture, the solvent was distilled off, and 0.26g of specified substance was obtained.
0118 1H-NMR(CDCl3): 2. -- 49 and 2.51 (3 H;s) -- 3.11 (2 H;dd, J= 16.6, 14.0Hz) 3.40 (3 H;s), 3.91 (1 H;t, J= 5.6Hz), -- 7.19-7.63 (4 H;m) (5) N- **(1S)-1-cyclohexyl methyl-2-hydroxy-3- (1-methyl-5-tetra-ZORIRU) By the same actuation as the thio propyl**-2-(3S) (-2, 3-dihydro - 1, 5-dimethyl-2-oxo--1H-1, 4-benzodiazepine-3-IRU) acetamido example 13 (8) 2-(2, 3-dihydro - 1, 5-dimethyl - 2-oxo--1(H)-benzodiazepine-3-IRU) acetic acid was used instead of 2-(2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) acetic acid, and the specified substance was obtained with 51% of yield.
0119 1H-NMR(CDCl3): 0.81-0.97(3H;m), 1.12-1.28(5H;m), 1.37-1.44(1H;m), 1.61-1.67(3H;m), 1.80(1H;d,J=19.6Hz), 2.48,2.49(3H;s), 2.92-3.04(2H;m), 3.34(3H;s), 3.37-3.47(1H;m), 3.93(3H;s), 3.99(1H;bs), 4.15(1H;bs), 4.56(1H;bs), 6.93(1H;d,J=9.6Hz), 7.23-7.30(2H;m, 7.497.54(2 H;m) MS(FAB, Pos.): 514 (M-H+D +1) examples 282- () (3S)-5-benzyl -2, 3-dihydro-1-methyl-2-oxo--1H-1, and 4-benzodiazepine-3-IRU-N-**(1S) -1-cyclohexyl methyl-2-hydroxy-3-(1-methyl-5-tetra-ZORIRU) thio propyl** acetamido (1) N-t-butyloxy carbonyl-L-asparatic acid alpha-2-(1-oxo-phenethyl) ANIRAMIDO By the same actuation as beta-benzyl ester example 27 (1) 2-(1-oxo-phenethyl) aniline was used instead of 2-amino benzophenone, and the specified substance was obtained with 25% of yield.
0120 1H-NMR(CDCl3): 1.40(9H;s), 2.79(1H;dd,J=16.2,5.4Hz), 3.30(1H;dd,J=13.5,5.4Hz), 4.31(2H;s), 4.69-4.73(1H;m), 5.10(2H;q,J=10.8Hz), 5.78(1H;d,J=10.8Hz), 7.12(1H;t,J=10.8Hz), 7.20-7.36(5H;m), 7.30(5H;s), 7.52(11H;t,J=10.8Hz), 8.01(1H;d,J=10.8Hz), 8.76(1H;d, J= 10.8Hz, 12.46(1 H;bs) MS (FAB, Pos.) : 517 (M+1) (2) benzyls By the same actuation as 2-(5-benzyl -2, 3-dihydro - 2-oxo--1(H)-benzodiazepine-3-IRU) acetate example 27 (2) N-t-butyloxy carbonyl-L-asparatic acid It is N-t-butyloxy carbonyl-L-asparatic acid instead of alpha-2-benzophenone amide beta-benzyl ester. alpha-2-(1-oxo-phenethyl) ANIRAMIDO beta-benzyl ester It used and the specified substance was obtained with 100% of yield.
0121 1 H-NMR (CDCl3) : 3.02-3.58 (2 H;m), 3.91-4.31 (2 H;m), 4.11-4.34 (1 H;m), 5.16 (2 H;s), 6.90-7.61 (4 H;m), 7.15 (5 H;s), 7.33 (5 H;s), 7.98(1 H;s) MS (EI, In Beam) : 397 (M-1) (3) Benzyl By the same actuation as 2-(5-benzyl -2, 3-dihydro-1-methyl - 2-oxo--1(H)-benzodiazepine-3-IRU) acetate example 14 (1) Benzyl 2- () (3S) -2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU acetate and benzyl 2- () (3R) It is benzyl instead of the equivalent mixture of -2, 3-dihydro-2-oxo--5-phenyl-1H-1, and 4-benzodiazepine-3-IRU acetate. 2-(5-benzyl -2, 3-dihydro - 2-oxo--1(H)-benzodiazepine-3-IRU) acetate It used and the specified substance was obtained with 40% of yield.
0122 1 H-NMR (CDCl3) : 3.29 (1 H;dd, J= 72.9, 16.2Hz), 3.32 (1 H;dd, J= 72.9, 16.2Hz) 3.97-4.16 (3 H;m), 5.12 (2 H;s) 7.06-7.52 (9 H;m), 7.32(5 H;s) MS (EI, In Beam) : 412 (M+) (4) By the same actuation as 2-(5-benzyl -2, 3-dihydro-1-methyl - 2-oxo--1(H)-benzodiazepine-3-IRU) acetic-acid example 27 (4) Benzyl 2- (2, 3-dihydro - 1, 5-dimethyl - 2-oxo--1(H)-benzodiazepine-3-IRU) It is benzyl instead of acetate. 2-(5-benzyl -2, 3-dihydro-1-methyl - 2-oxo--1(H)-benzodiazepine-3-IRU) acetate It used and the specified substance was obtained with 88% of yield.
0123 1 H-NMR (CDCl3) : 3.11 (1 H;d, J= 8.1Hz), 3.29 (3 H;s) 3.96 (1 H;t, J= 5.4Hz),

4.06-4.20 (1 H;m), 4.11 (2 H;d, J= 5.4Hz), 7.09 (1 H;d, J= 5.4Hz) 7.16-7.27 (6 H;m), 7.49 (1 H;t, J= 8.1Hz), 7.59(1 H;d, J= 5.4Hz) MS () **EI, In** Beam: 322 (M+) (5) 2- () The (3S)-5-benzyl -2, 3-dihydro-1-methyl-2-oxo--1H- 1 and 4 -- by the same actuation as the -benzodiazepine-3-IRU-N-**(1S) -1-cyclohexyl methyl-2-hydroxy-3-(1-methyl-5-tetra-ZORIRU) thio propyl** acetamido example 13 (8) Instead of 2-(2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) acetic acid, 2-(5-benzyl -2, 3-dihydro-1-methyl - 2-oxo--1(H)-benzodiazepine-3-IRU) acetic acid It used and the specified substance was obtained with 57% of yield.

0124 1H-NMR(CDCl3): 0.80-0.98(3H;m), 1.13-1.26(4H;m), 1.36-1.42(1H;m), 1.54-1.66(4H;m), 1.77(1H;d,J=12.0Hz), 2.99(1H;dd,J=35.2,6.8Hz), 3.03(1H;dd,J=35.2,6.8Hz), 3.23(3H;s), 3.89-4.11(2H;m), 3.92(3H;s), 4.01(1H;t,J=6.0Hz),4.11(2H;dd,J=41.2, 14.4Hz), 4.39(1 H;s, 6.92 (1 H;d, J= 9.2Hz), 7.09 (2 H;d, J= 7.2Hz) 7.14-7.22 (4 H;m), 7.43 (1 H;t, J= 8.0Hz), 7.55 (1 H;d, J= 8.0Hz) MS(FAB, Pos.): 590 (M+1) examples 29N-**(1S)-cyclohexyl methyl-2-hydroxy-3-(1-methyl-5-tetra-ZORIRU) thio propyl**-2-(3S) (-2, 3-dihydro-1-methyl-2-oxo--5-phenethyl-1H-1, 4-benzodiazepine-3-IRU) acetamido (1 - -) N-t-butyloxy carbonyl-L-asparatic acid alpha-2-(1-oxo--3-phenylpropyl) ANIRAMIDO By the same actuation as beta-benzyl ester example 27 (1) 2-(1-oxo--3-phenylpropyl) aniline was used instead of 2-amino benzophenone, and the specified substance was obtained with 44% of yield.

0125 1H-NMR(CDCl3): 1.46,1.55(9H;s), 2.75-2.87(1H;m), 2.99-3.13(2H;m), 3.30-3.37(2H;m), 4.64-4.76(1H;m), 5.06-5.24(2H;m), 5.84(1H;d,J=10.8Hz), 7.09(1H;t,J=8.1Hz), 7.22-7.33(4H;m), 7.31(5H;s), 7.46-7.61(2H;m), 7.87(1H;d,J=5.4Hz), 8.73(1H;d,J=5.4Hz), 12.48(1 H;bs) MS (EI, In Beam) : 530 (M+) (2) Benzyl By the same actuation as 2-(2 and 3-dihydro-2-oxo-- 5-phenethyl-1(H)-benzodiazepine-3-IRU) acetate example 27 (2) N-t-butyloxy carbonyl-L-asparatic acid alpha-2-benzophenone amide It is N-t-butyloxy carbonyl-L-asparatic acid instead of beta-benzyl ester. alpha-2-(1-oxo--3-phenylpropyl) ANIRAMIDO The specified substance was obtained with 100% of yield using beta-benzyl ester.

0126 (3) Benzyl By the same actuation as 2-(2 and 3-dihydro-1-methyl-2-oxo-- 5-phenethyl-1(H)-benzodiazepine-3-IRU) acetate example 14 (1) Benzyl 2- () (3S) -2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU acetate and benzyl 2- () (3R) -2, It is benzyl instead of the equivalent mixture of 3-dihydro-2-oxo--5-phenyl-1H-1 and 4-benzodiazepine-3-IRU acetate. 2-(2 and 3-dihydro-2-oxo-- 5-phenethyl-1(H)-benzodiazepine-3-IRU) acetate It used and the specified substance was obtained with 56% of yield.

0127 1 H-NMR (CDCl3) : 2.85 (2 H;t, J= 8.1Hz), 3.05 (2 H;d, J= 8.1Hz) 3.10 (1 H;dd, J= 16.2, 8.1Hz), 3.28 (3 H;s) 3.40 (1 H;dd, J= 16.2, 8.1Hz), 4.00 (1 H;t, J= 8.1Hz) 5.11 (2 H;dd, J= 10.8, 16.2Hz), 7.06-7.50 (9 H;m), 7.32(5 H;s) MS (EI, In Beam) : 426 (M+) (4) By the same actuation as 2-(2 and 3-dihydro-1-methyl-2-oxo-- 5-phenethyl-1(H)-benzodiazepine-3-IRU) acetic-acid example 27 (4) Benzyl 2- (2, 3-dihydro - 1, 5-dimethyl - 2-oxo--1(H)-benzodiazepine-3-IRU) It is benzyl instead of acetate. 2-(2 and 3-dihydro-1-methyl-2-oxo-- 5-phenethyl-1(H)-benzodiazepine-3-IRU) acetate It used and the specified substance was obtained with 100% of yield.

0128 (5) N- **(1S)-cyclohexyl methyl-2-hydroxy-3- (1-methyl-5-tetra-ZORIRU) By the same actuation as the thio propyl**-2-(3S) (-2, 3-dihydro-1-methyl-2-oxo--5-phenethyl-1H-1, 4-benzodiazepine-3-IRU) acetamido example 13 (8) Instead of 2-(2, 3-dihydro-2-oxo--5-phenyl-1H-1, 4-benzodiazepine-3-IRU) acetic acid, 2-(2 and 3-dihydro-1-methyl-2-oxo-- 5-phenethyl-1(H)-benzodiazepine-3-IRU) acetic acid It used and the specified substance was obtained with 50% of yield.

0129 1 H-NMR (CDCl3) : 0.89-1.92 (13 H;m), 2.94-3.15 (6 H;m), 3.17-3.26 (2 H;m), 3.36 (3 H;s), 3.54-3.60 (2 H;m), 3.97-4.12 (1 H;m), 4.03 (3 H;s), 4.26 (1 H;bs), 7.08-7.37 (7 H;m), 7.56-7.62(2 H;m) MS (FAB, Pos.) : 604 (M+1) **0130**

Formula 7

0131
Table 1

EXHIBIT A

0132

Table 2

EXHIBIT A